TECHNICAL
REPORT

Health Status and Medical Treatment of the Future Elderly

Final Report

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PREFACE

To help the government take the actions necessary to keep the Medicare trust funds solvent, the Centers for Medicare and Medicaid Services (CMS) must generate accurate projections of current and future health care spending. Also critical is to understand the key biomedical breakthroughs and demographic trends that are likely to occur and that might affect health and spending outcomes. At the request of CMS, RAND researchers developed a demographic-economic model framework of health care spending projections, called the Future Elderly Model, that allows microsimulations to be used to ask and answer what-if questions about the effects of changes in health status on future health care costs. This report documents the results of the project in terms of projected biomedical breakthroughs, disease and disability outcomes, and expenditures among the elderly from the year 2000 through 2030.

Study findings should be of interest to the CMS Office of the Actuary, health policy planners, and health economists. Those interested in biomedical advances and their likely effect on the elderly may also have an interest in the findings.

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CONTENTS

FIGURES

TABLES

SUMMARY

The Centers for Medicare & Medicaid Services (CMS) must generate accurate predictions of future spending for planning purposes. To investigate a better method for understanding how medical breakthroughs and demographic trends will affect future Medicare costs, CMS contracted with RAND to develop models to project how changes in health status, disease, and disability among the next generation of elderly will affect future spending.

BACKGROUND

Predictions of future health care spending necessitate estimating the number and sociodemographic characteristics of future beneficiaries who will be alive in each subsequent year and the likely magnitude of their health care spending. The official projections of the aged beneficiary population by age and sex currently used by CMS are taken from the Trustees' Reports of the Social Security Administration (SSA). These projections already take into account two long-term trends: a decrease in age-specific mortality rates and a significant increase in the over-65 population that will begin in the year 2012, due to the aging of the baby boomers.

However, estimating future health care costs is more difficult. To improve their current projections of health care costs, CMS would like to rely on more accurate estimates of future health care needs and expenditures. Estimates of future health expenditures for an individual of a given age are full of uncertainty. Individual health care spending is a function of many factors: age, sex, health status, diseases and the medical technology used to treat them, the price of care, insurance coverage, living arrangements, and care from family and friends. Per capita estimates of spending are uncertain because they depend on hard-to-predict changes in all these factors. Existing models do not attempt to forecast specific treatment changes that will affect health status and future expenditures or trends in other key factors.

The trend that may be most controversial (with respect to its potential effect on future health expenditures) is the apparent delay in morbidity: many people are staying healthy to older ages. As a consequence of this trend, it has been theorized that the attendant functional limitations and costs of morbidity may be compressed into the last few years of life, which could reduce health care costs. However, the savings expected from compressed morbidity might be offset by the effect of another trend, that is, reduced mortality or extended life expectancy.

Current models account for the added cost of greater longevity that would result from reduced mortality, but such models tend to assume that health (good or bad) is a permanent state. However, studies of particular diseases find that mortality gains follow from lifestyle changes, primary and secondary disease prevention, and dramatic improvements in treatment. These same factors can result in a postponement of disease, disability, and proximity to death, i.e., a compression of morbidity. Thus, the same factors that are expected to raise health care costs by increasing life expectancy might also serve to limit costs by delaying morbidity. As a result,

lower mortality rates might have less effect on expenditures than current models would predict, although, clearly, not all treatment advances postpone the need for medical care.

The primary objective of the present study was to develop a demographic-economic model framework of health care spending projections that will enable CMS actuaries and policymakers to ask and answer what-if questions about the effects of changes in health status and disease treatment on future health care costs. The model answers the following types of questions:

- What are the future health expenditures for Medicare likely to be during the next 25 years if the trends in morbidity and mortality of the last decade are taken as projections into the next decade, and if disability among the elderly declines at a steady rate?
- How will the growth of future health care expenditures for the elderly be affected by advances in the development of new diagnostic tools, medical procedures, and new medications for chronic and fatal illnesses?
- How will the sociodemographic characteristics of the next generation of elderly individuals affect future health care spending?

STUDY DESIGN AND METHODS

The study was conducted in four phases. Phase I consisted of a literature review, Phase II was a technical expert panel (TEP) assessment, Phase III included the development of the model, and in Phase IV, we applied the model to various what-if scenarios.

Literature Review

During Phase I, we reviewed the current literature on trends in the health and functional status of the elderly, the likely effects of new medical advances and treatments on morbidity and mortality among the elderly, and the likely costs of new medical treatments. In what we will refer to as the social science literature review, we also reviewed past efforts to model the effects of changes in health status, risk factors, and treatments on health care expenditures.

Expert Panel Assessments

During Phase II, we convened TEPs to provide guidance on the likely future advances in the medical treatment of specific illnesses and the early detection and prevention of diseases. We used a modification of the technical expert panel method developed at RAND to convene four separate panels targeted at specific clinical domains: cardiovascular disease, the biology of aging and cancer, neurological disease, and changes in health care services. Using our literature reviews, past experience with expert panels, and the advice of local experts, we selected individuals who represented a broad range of clinical and basic science expertise.

The technical experts were surveyed to identify what they considered the leading potential medical breakthroughs in each area, considering factors of potential effect and cost. Based on

these responses and our preliminary literature review, we selected a number of potential breakthroughs in each of the four areas for further, in-depth review using the procedures of evidence-based research. For each breakthrough, we identified the current developmental status and potential barriers to implementation.

As part of Phase II, we also convened a fifth expert panel composed mainly of social scientists from the fields of demography, epidemiology, health economics, actuarial science, and operations research. The role of this panel was to help us determine the appropriate health status measures and methodologies and to identify data sets for estimating model parameters as well as the best modeling techniques.

Development of the Future Elderly Model

During Phase III, with the guidance of our social science technical expert panel, we developed a demographic-economic model, the Future Elderly Model (FEM). The FEM is a microsimulation model that tracks elderly, Medicare-eligible individuals over time to project their health conditions, their functional status, and ultimately their Medicare and total health care expenditures. The FEM was intended to serve two purposes: First, it was to be used to answer the question, If current health status and disability trends continue, what will be the costs to Medicare for treating the elderly? Second, it was to be used to simulate and evaluate a variety of scenarios regarding the future health care environment. The FEM we developed actually combined three individual models: a model of health care costs, a model of health status transitions, and a model to predict characteristics of future, newly-entering Medicare enrollees (the "rejuvenation" model).

Data. The FEM started with data from the Medicare Current Beneficiary Survey (MCBS), which includes a nationally representative sample of aged, disabled, and institutionalized Medicare beneficiaries, as the host data set (the data set included individuals who turned 65 and participated in the MCBS from 1992 through 1998). The MCBS is an interview survey designed to ascertain utilization and expenditures for the Medicare population, particularly expenditures borne by the beneficiary or by supplemental insurance. The survey sample is interviewed some 12 times over a three-year period. The data set contains detailed self-reported information on height, weight, the prevalence of various conditions, measures of physical limitations in performing activities of daily living and instrumental activities of daily living, and health service use, as well as Medicare service use records. The sample size for individuals 65 and older in 1998 with complete records was 10,881. Each sample member's data are weighted to take into account the number of beneficiaries in the Medicare population that member represents.

Because we were studying transitions, our data set included only MCBS respondents who participated in two or more consecutive survey waves. The outcome measure was based on pairs of consecutive interviews. In order to ensure that we were examining the transition from positive health status to a disease state, we included only individuals who did not report a specific condition at the initial interview—i.e., among people without a condition, we modeled the likelihood that they developed the condition in the following year.

Health status transition model. The FEM then predicts the health conditions and functional status of the baseline sample for the next year (reweighting to match the health status trends from the National Health Interview Survey [NHIS] and the Census population projections). To project the health transitions, a discrete piecewise linear hazard model was estimated. The hazard of getting a disease and dying depends on risk factors (gender, education, race, ethnicity, education, obesity, ever having smoked); other conditions if medically warranted; functional status; and age (piecewise linear spline, node at age 77). The model did not control for household income or for current smoking behavior, since doing so would require projection models of future income and smoking behavior, respectively. A similar model was used to predict functional status and nursing home residency. We treated all health states as "absorbing"—i.e., once people got an illness, they had it forever and therefore could not get it again—and modeled transitions into the states. This assumption was consistent with the way the data were obtained ("Has a doctor ever told you....") and with the course of most of the chronic diseases (diabetes, heart disease, etc.). However, for some conditions or outcomes, such as altered functional status, recovery is possible; therefore, the hazard model would overestimate their prevalence.

Sample rejuvenation. As our initial sample ages, it becomes less representative of the entire over-65 population; thus, we rejuvenated our sample yearly (through 2030) with a newly entering cohort of 65-year-olds.

Cost modeling. Finally, the FEM predicts costs. The cost estimations were based on pooled weighted least squares regressions with total Medicare reimbursement and total health care reimbursement as the dependent variables; and health status measures, self-reported disease categories, and interactions of health measures and disease conditions as the independent variables. The model was calibrated to replicate the total health care and Medicare expenditures for the elderly sample represented by the MCBS.

All FEM costs are in 1998 dollars and are adjusted for inflation, but not for cost of living and changes in the economy. The FEM does not include supply-side factors (e.g., physician supply) or changes in insurance coverage. We dropped Medicare HMO enrollees and assumed that all Medicare beneficiaries were covered under the Medicare Fee-for-Service (FFS) system in our estimation, which may overestimate the total costs if HMOs actually save money compared to FFS. The FEM also does not model the shifts from inpatient to outpatient services. Finally, we assumed that every beneficiary had both Medicare Part A and Part B in predicting future Medicare costs.

We chose health status measures to meet several competing goals. First, we needed measures that could be used to predict costs. Second, our measures had to capture clinically relevant diseases that would be useful for predicting the effects of the breakthrough technologies. Third, the measures had to be readily available in the MCBS and any other data sets we would use to provide estimates for the microsimulation, for example, the NHIS. The health status measures were based on self-reported health conditions and disability. The conditions on which we decided to focus were the ones selected earlier by our expert panels as having the greatest potential for breakthroughs; these conditions are also the ones most prevalent in the elderly population and the most costly to treat. The models were integrated by first estimating costs for

the representative cohort. We then "aged" them one year using the health status model, introduced the new 65-year-olds, and then estimated costs again. This process was repeated for each year until a terminal date was reached.

The What-If Scenarios

Finally, during Phase IV, we considered the implications of a number of potential health care scenarios suggested by the experts—including potential breakthrough technologies as well as changes in lifestyle and the health care system—by exploring changes in the parameters of the model via what-if modeling.

Evaluating the Usefulness of the FEM to the Office of the Actuary

To evaluate the usefulness of the FEM, we focused on five components: the population projection, expenditure projections, econometric methodology, the what-if modeling, and the overall usefulness.

RESULTS

The Potential Breakthroughs

Lists of suggested breakthroughs in future health care were developed based on our literature reviews. Using these lists and the nominal group process, our technical expert panels identified 33 key potential breakthroughs for further review. These breakthroughs spanned the areas of improved disease prevention, more precise risk stratification and earlier detection of subclinical diseases through improved imaging and genetic profiling; better treatment for established diseases through biomedical engineering, cell biology, and genetic engineering; and changes in lifestyle and care management. For each breakthrough, the panels assessed the eligible (target) patient population, likelihood of implementation within 10 and 20 years, effect, and cost. The breakthroughs are listed in Table S.1.

Table S.1. Potential Medical Breakthroughs Identified by Technical Expert Panels

Disease	Likelihood of Occurrence at 20 years[a] (%)	Brief Summary of Effect
Cardiovascular Diseases		
Improved Disease Prevention	40	90% reduction in CVD.
Noninvasive Diagnostic Imaging to Improve Risk Stratification		Better identification of high-risk patients, leading to effective risk reduction strategies.
• General Population >45	15	
• Subclinical Disease	75	
• Clinical Disease	50	
Magnetic Resonance Angiography (as a replacement for coronary catheterization)	100	Replacement for conventional coronary angiography, likely to increase the number of persons undergoing the procedure.
Intraventricular cardioverter defibrillators		Life expectancy for people with congestive heart failure (CHF) is shifted by 6–10 months, 20% now die of some other cause.
• Clinical Disease	30-40	
Left Ventricular Assist Devices (LVAD)	50	General increase in function for persons with functional limitations, 50% decrease in heart failure-related hospitalizations, 20% of patients will have improved 1 year mortality.
Xenotransplants	1–3	Possibly similar to the benefit from human heart transplants, but several experts thought the effect would be lower as the population affected is likely to be different.
Therapeutic Angiogenesis		Little effect on mortality, decreased number of revascularization procedures by 20–30%.
• Clinical disease: augmentation for revascularization	Currently used	
• Clinical disease: replacement for revascularization	10	
Transmyocardial Revascularization	0–5	Little effect on mortality, decreased number of revascularization procedures by 20–30%.
Pacemaker/Defibrillators to Control Atrial Fibrillation	50	Decreased stroke by 50% of the attributable fraction due to atrial fibrillation (AF).

Table S.1. Potential Medical Breakthroughs Identified by Technical Expert Panels

Catheter-based Ablation Techniques to Control Atrial Fibrillation	20	Decreased stroke by 50% of the attributable fraction due to AF.
Disease	**Likelihood of Occurrence at 20 years[a] (%)**	**Brief Summary of Effect**
Biology of Aging and Cancer		
Telomerase Inhibitors	100	Mortality: 50% will be cured; 50% will have a 25% prolongation of life.
Cancer Vaccines	10–20	Melanoma/renal cell carcinoma could be cured. All other cancers could have a 25% boost in survival.
Selective Estrogen Receptor Modulators (SERMS)	90	Breast cancer decrease of approximately 30%, decreased osteoporosis (increase bone density in spine of osteoporotic women by 2%).
Antiangiogenesis	70–100	Cure for metastatic disease in 10–50%.
Diabetes Prevention via Drugs that Enhance Insulin Sensitivity	65	50% prevention in Type 2 over >10–15 years.
Compounds that Extend Life Span	0–50	10–20 years of extra life of an equivalency between 20 and50 years of age.
Compounds that Improve Cognition	20	Decrease in traffic accidents due to reflex ability, decrease in pedestrian accidents due to reflex ability, increased period of participation in the workforce.
Neurological Diseases		
Improved Identification of Persons at Risk for Alzheimer's Disease	30	No direct effect on mortality or morbidity, but it will identify people at higher risk for guided treatment.
Primary Prevention of Alzheimer's Disease Using Therapies Based on the Amyloid Hypothesis	40	Delay of onset by median 5 years (range 3–10 years), slow progression by a mild to moderate amount.
Primary Prevention of Alzheimer's Disease Using Existing or Other New Drugs	40	Delay of onset by 2–5 years, minor effect on progression.

Table S.1. Potential Medical Breakthroughs Identified by Technical Expert Panels

Treatment of Established Alzheimer's Disease by Vaccine, Secretase Inhibitor, Antioxidants, Anti-inflammatories, or SERMS	30	Decrease in rate of progression that is mild to moderate.
Treatment of Established Alzheimer's Disease by Cognition Enhancers	40	Shifts back in time by 6 months to 2 years but does not modify the disease.
Prevention and Treatment of Parkinson's Disease by Profiling Genetic Predisposition for Susceptibility to Environmental Toxins	10	Eliminates disease in 15% of existing cases, delays onset in 15–20% of cases.
Treatment of Parkinson's Disease Therapies by Neurotransplantation	25	Shifts back in time by 2 to 5 years but does not modify disease.
Treatment of Acute Stroke by Drugs that Minimize Cell Death	60	Decrease in disability due to stroke of median 30% (range 25–50%).
Treatment of Acute Stroke by Stem Cell Transplant	20	Decrease in disability due to stroke of 25%.
Improved Treatment of Depression Using New or Existing Drugs	70	70% improvement in symptoms (e.g., 35% improvement over placebo).
Health Services		
Increasing the Use of Known Interventions		
• Everybody	80	Very high, approximately equivalent to improving the control of hypertension by 25–50%.
• Chronic Disease Group	90	Very high.
Care Coordination	90	Modest. Approximately equivalent to improving the control of hypertension by 5–10%. Change on function will be slight if at all. Main benefit will be on utilization.
Improved Detection of Under-diagnosed Conditions		Improvement in outcomes for undiagnosed approximately the same as existing evidence for diagnosed patients.
• Depression	30	
• Diabetes	50	
• Dementia	30	
Better Medication Management	100	Moderate sized effect on reduced hospitalization/shortened stay, decreased mortality, and increased function.

Table S.1. Potential Medical Breakthroughs Identified by Technical Expert Panels

Environmental Improvements to Assist with Lifestyle Change and Chronic Disease Self-management	85	For people with chronic disease similar to chronic management programs to decrease utilization.

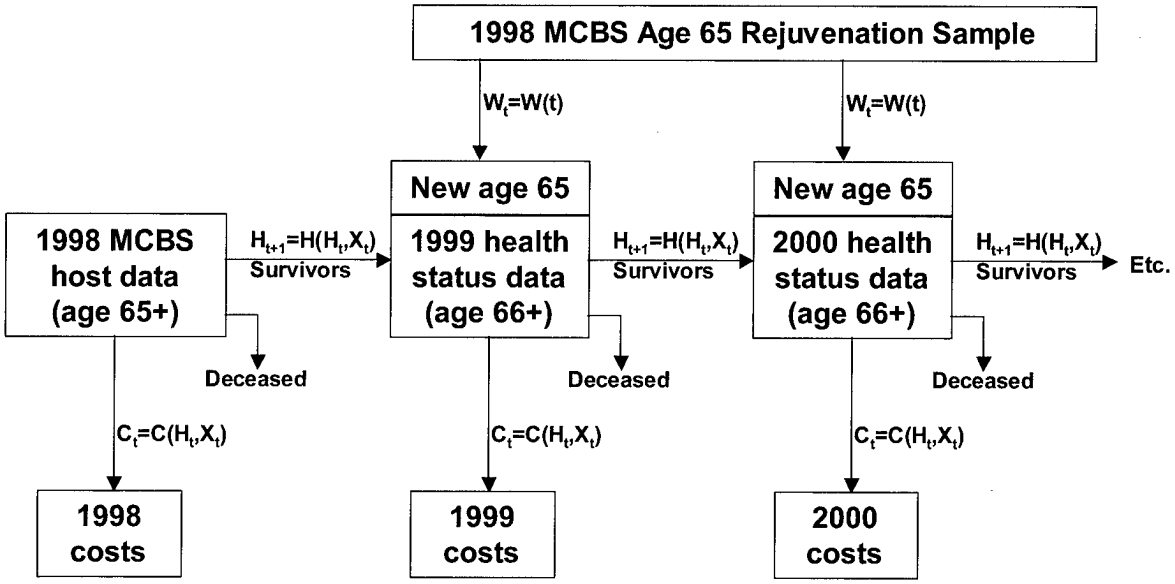
[a] Likelihood of occurrence means widespread use in clinical practice.

The Future Elderly Model

The FEM differs from traditional approaches in that it includes a multidimensional characterization of health status and it is not cell-based. This allows us to include a richer set of demographic controls as well as comorbid conditions and functional status.

The first step in creating our microsimulation model was to estimate health transition models for each individual. We then estimated future health transitions. We then brought in a new cohort of 65-year-olds (rejuvenation) and estimate costs for everyone. Figure S.1 depicts how the cost models, transition models, and rejuvenation models are integrated into the microsimulation model.

Figure S.1. Overview of the FEM Model



NOTES: 1. C = costs; C_t = costs in a given calendar year; H = health status; H_t = health status during the year of the interview; W = a relative weight; X_t = demographic controls. 2. Costs are predicted in constant (1998) dollars and assume a level of treatment and technology as it existed in the 1990s.

We assessed the baseline health care characteristics for the cohort of individuals age 65 and older in the 1998 MCBS data set and used these findings to predict per capita expenditures for that year. We then assessed the yearly health and functional status and projected the conditions and health care costs of the survivors for each subsequent year. As people became deceased, they were removed from the cohort. Likewise, each year, the sample was rejuvenated by the addition of a pool of new beneficiaries who turned 65.

Determinants of Health Care Expenditures (the Cost Model)

Using MCBS data, we explored how alternative measures of health and disability affect expenditures. Reporting one or more functional limitations (assessed as activities of daily living

[ADL]), residing in a nursing home, and having one or more chronic diseases were associated with higher expenses. Likewise, self-reported health status was highly correlated with health expenditures; however, the social science TEP cautioned us against considering this measure for a forecasting model, as treatment breakthroughs are difficult to translate into changes in self-reported health status.

Our final cost model also included demographics and measures of physical health. Demographics included such factors as age, gender, ethnicity, education, and geographical area of residence. Measures of physical health included self-reported health status, ADL categories (including nursing home residence), chronic diseases, and interactions of these measures.

Ever having smoked, residing in the Northeast, mortality, obesity, and physical health status (measured by number of ADLs and admission to nursing home) had considerable effects on expenditures. Consistent with the literature, individuals who die during the year have substantially higher medical expenses than survivors. Medical expenditures increase with age, until about age 85. Lower expenditures among the oldest elderly may reflect biological differences among those who have survived to that age as well as less aggressive medical treatment. We also find that costs increase substantially with ADLs, particularly with three or more. The interactions of ADLs and disease vary in magnitude and significance, in both this model and others.

Determinants of Health Status: The Health Status Transition Model

Using the Health Status Transition Model revealed a set of factors that increase the risk for a variety of chronic conditions, decreases in ADLs, and nursing home residence:

- Men tend to have higher risks of cancer and heart disease and lower risks of hypertension, arthritis, and disability than do women.
- Blacks and Hispanics have higher risks of hypertension than do Caucasians.
- Hispanics also have higher risks of diabetes than do Blacks or Caucasians.
- Hispanics are far less likely than non-Hispanics to enter a long-term care facility such as a nursing home.
- Better-educated individuals tend to be in better health.
- Having ever smoked increases the risk of cancer, stroke, lung disease, and disability, but not by very much and only marginally significantly for cancer.
- Co-occurrence of two or more health conditions tended to increase the risk for certain other conditions significantly, for example, diabetes and hypertension significantly increased the risk of developing a heart condition.

We also estimated the effect of a variety of health conditions on the risk for mortality. Cancer, heart disease, stroke, Alzheimer's disease, lung disease, and disability (low ADL score)

were associated with an increased risk of mortality, whereas arthritis was associated with a decreased risk.

The Health Status of Future Medicare Users

Using data from the NHIS, we then created a model to predict the health status of future cohorts of Medicare beneficiaries between the years 2001 and 2030. We considered seven of the chronic conditions most prevalent among the elderly—heart disease, hypertension, cerebrovascular disease, Alzheimer's disease, cancer, diabetes, and chronic obstructive pulmonary disease—as well as physical disability. Unfortunately, the NHIS provides each age cohort with a unique list of conditions from which to choose; thus, respondents cannot select the conditions they have had from the full list of conditions.

Our prediction strategy consisted of four steps. In the first step, we used the NHIS data to obtain age-specific prevalence rates for the conditions of interest. These prevalence rates were smoothed using the overlap polynomial method to produce noise-free estimates of the incidence of low-prevalence diseases. In the second step, we used a synthetic cohort approach to estimate an age-incidence profile for each disease from the smoothed prevalence estimates. In the third step, we used the prevalence and incidence functions to generate our projections of the health status of future Medicare-entering cohorts. The method is based on the idea that for any given future year, we know the current age of the entering cohort for that year. Finally, in the fourth step, we constructed population-weighted estimates to predict the co-occurrence of several diseases in the same individuals, in order to predict future expenditures more accurately.

Consideration of Future Scenarios

We modified our FEM to simulate the effect on expenditures of a variety of likely scenarios or breakthroughs proposed by our expert panels. We then compared projected expenditures without the scenarios or breakthroughs (the "baseline" situation) with our estimates of expenditures following the breakthroughs over the course of the first 30 years of the 21st century. To assist in this effort, the expert panels identified eligible populations, likelihoods of occurrence, costs, and estimates of effect on morbidity and mortality for most of the technologies.

The use of telomerase inhibitors (TI) to treat cancer. We modeled the potential effects of the use of a class of cell-replication inhibiting chemicals known as telomerase inhibitors (TI) to treat cancer. Our model suggested that TI would reduce the prevalence of cancers considerably: those who received treatment and were cured or whose cancer was controlled would experience an increase in life expectancy. Although TI would increase total expenditures on the elderly, they would not greatly increase Medicare spending. However, we did not consider several factors, such as cancer type: TI works only on solid tumors and less well on metastatic cancer than on localized cancer.

The use of cancer vaccines. We also modeled the possible effects of the introduction of a cancer vaccine that could be used against all types of cancers. Cancer vaccines would have a large effect on cancer prevalence while modestly increasing Medicare costs, largely due to

prolongation of life. However, we did not include the potential effect on melanoma in our simulation: because it is expected that the vaccines could cure melanoma, their effect on prevalence and related expenditures for all cancers would likely be larger than our results suggest.

The use of a drug to prevent diabetes. The third scenario we modeled was the use of an insulin sensitization drug to prevent type 2 diabetes. It is expected that of the 80 million obese people (obesity being defined as a body mass index over 30) in the United States, some 10 percent will develop type 2 diabetes; we assumed that 30 percent of elderly obese people would develop diabetes. The prevalence of diabetes among the elderly is expected to rise by about 12 percent from 2001 to 2030. Over five years, our model showed, the drugs would prevent over 50 percent of new cases of diabetes. Making a number of assumptions, such as a reduction of 65 percent over ten years and a treatment rate of only 30 percent (with random targeting of treatment), we found only modest effects. The drug would reduce prevalence by only about 1 percent, in part due to the large size of the obese diabetic population. The drug had little effect on Medicare expenditures, particularly over the long term where the drug would be expected to increase life expectancy.

The effect of extending lifespan. We modeled the possible effect of a not-yet-identified compound that would extend life span by mimicking the effects of long-term reduction in caloric intake. This scenario is based on findings from the 1970s that chronically reducing rodents' energy intake prolonged their lives. According to our simulation, if begun early enough (around the age of 35), the treatment would extend life expectancy by 10 to 20 years. With no concomitant improvements in health status, disease prevalence and Medicare costs would increase substantially. However, based on the findings from the animal model, the incidence of several diseases, including cardiovascular disease and some types of cancer, is reduced or at least delayed, raising the prospect of compressed morbidity and its attendant costs.

The effect of increasing education level. We also modeled the potential effect of an increase in the average level of education of the future Medicare population. We considered two possible scenarios: 1) after 2002, everyone who became Medicare-eligible had a college degree, or 2) after 2002, the education level of each Medicare-eligible person increased one level (for example, persons with some high school education became high school graduates and high school graduates now had some college education). Whereas neither scenario was realistic, they showed how the FEM incorporated information about education and could be used to project the effect on health status, Medicare expenditures, and total health care costs. Increasing educational attainment resulted in a decrease in death rate and in the prevalence for a number of diseases but higher Medicare and total expenditures; however, the differences in expenditure were small.

The effect of changing ethnicity. We modeled the possible effects of a continued increase in the Hispanic population. Between 2000 and 2030, the proportion of the U.S. population that is made up of Hispanics is expected to grow from 11 percent to 19 percent. This increase is expected to result in an increased mortality rate; an increase in the prevalence of particular diseases, such as heart disease, diabetes, arthritis, and hypertension; and a decrease in the prevalence of cancer, stroke, lung disease, and nursing home use. However, our simulation assumed that the future Hispanic population would have demographic and socioeconomic status similar to the current Hispanic population.

The effect of decreasing smoking rates. We modeled the potential effect of a decrease in the rate of smoking among new Medicare beneficiaries. Our assumption was that no one entering Medicare after 2002 ever smoked. From 2002 to 2030, the overall death rate among Medicare beneficiaries would decrease by 4.3 percent. Whereas the prevalence rates for a number of diseases would change (for example, the lung disease prevalence would fall by 8 percent) with the decrease in smoking, the decrease in mortality rate would also alter the disease prevalence. The reduction in smoking would result in a decrease in Medicare and total health care expenditures, with a savings to Medicare alone of $434 billion. Whereas this scenario is unrealistic, more modest decreases in the rate of smoking might still alter disease prevalence and Medicare expenditures; the FEM could be used to predict their magnitude.

The effect of decreasing obesity rates. We also modeled the potential effect of a decrease in the rate of obesity among Medicare beneficiaries. We considered two scenarios: no one entering Medicare after 2002 is obese and 2) after 2002, no Medicare beneficiary is obese. Neither scenario resulted in a decrease in the mortality rate. Nevertheless, the prevalence of a number of diseases, including arthritis, diabetes, and heart disease, decreased. Initial differences in the magnitude of the decreases between the two scenarios diminish over time as cohorts who entered prior to 2002 leave the population through death. Our model showed that the unrealistically extreme measure of eliminating obesity reduced Medicare and total expenditures only minimally, suggesting that more modest improvements in weight control would have a smaller effect.

The effects of changes in diagnosis and treatment of cardiovascular diseases. Finally, we modeled the application of eight different emerging technologies to the diagnosis and treatment of cardiovascular diseases. In this simulation, beneficiaries were randomly assigned to a treatment based on the probabilities estimated by the expert panel, and it was assumed that each beneficiary would receive only one such treatment. Our model showed that, with the exception of stroke, the disease prevalence was unaffected by the treatments; the prevalence of stroke decreased relative to the baseline. Nevertheless, the costs of treating cardiovascular diseases are likely to continue to increase over those of the baseline.

Evaluating the Usefulness of the FEM

We considered five aspects of the FEM in assessing its likely utility to the Office of the Actuary (OACT). These aspects included population projection, expenditure projection, econometric methodology, and what-if modeling.

Population projection. Population projections are based on starting population, mortality rates, migration, and fertility patterns (the latter two factors were disregarded for this report).

The FEM used Census data to determine the size of each entering cohort. In contrast, the population projection on which the OACT models are based is generated annually by the Office of the Actuary at the Social Security Administration (SSA). The SSA includes three populations excluded by the Census: those missed by the Census, those residing in territories and outlying areas, and military personnel and dependents residing overseas. Thus, SSA estimates of current population are higher than those of the Census. However, the FEM also assumes all individuals

65 years and older are covered by Medicare Parts A and B, resulting in a small (approximately 3 percent) overstatement of the Medicare population and costs.

The FEM and SSA estimates of mortality also diverge, due to differences in their projections of mortality improvement. The most recent SSA projections assume a decline in the death rate through the year 2030, based on a set of implicitly assumed medical advances and an analysis of historical trends in the causes of death. In contrast, the FEM baseline projections are based on MCBS data from the 1990s and no further improvement in medical technology or mortality rates.

Expenditure projections. We compared our projected expenditures based on the FEM to those of the Medicare Trustees' Report for 2002, making appropriate adjustments.

The FEM is based on four sets of projections with dependent variables for total Medicare expenditures, Medicare Part A payments, Medicare Part B payments, and Medicare Part A and Part B payments. However, the FEM model estimates per capita expenditures only for those with both Part A and Part B. The FEM also includes cases with less than 12 months enrollment (often due to death).

According to the CMS projections, Medicare expenditures will grow at a rate far exceeding that predicted by the FEM, even after adjusting for inflation and population growth. The central concept of the OACT baseline is that it is based on the scenario *most likely* to occur, according to general trends in morbidity and mortality and a number of implicit advances in medical technology that result in increased per capita costs. The FEM baseline assumes no changes in the underlying morbidity and mortality and maintenance of the status quo (no further advances) in medical technology. These conflicting concepts of baseline make any direct comparison between the two difficult. The modeling of a what-if scenario that mimics the assumptions in the OACT baseline would help bridge this gap.

Econometric methodology. The FEM modeled transitions into a variety of health states, using proportional hazards modeling. The transition probabilities are based on a variety of independent variables including age, sex, race, education, and other medical conditions. The results are consistent with epidemiological findings and clinical intuition.

What-if scenarios. The what-if scenarios summarized above illustrate one of the most useful features of the FEM to the Office of the Actuary, namely the ability to model the potential effects on future costs of a variety of hypothetical or likely trends in medical technology, health care services, and demographics. However, we realize that the current utility of the model is limited because of the differences in baselines and expenditure projections enumerated above.

Conceptually, these differences could be bridged by adopting specific scenarios in which the FEM-projected death rate decreases similarly to that projected by the SSA, using it as a baseline, and analyzing what-if scenarios relative to such a baseline. However, the work required to produce a suitable baseline would be substantial and the analytical problems to be overcome would be non-trivial.

Several other changes to the FEM would also make it more suitable to the OACT. These include modifying the calculations of Medicare costs (using the same categories of services as does CMS) and the choice of dependent variables.

CONCLUSIONS

This project served several purposes. First, it identified possible breakthroughs that could greatly affect the future health of and expenditures on behalf of the elderly. Second, we developed a microsimulation model that can be used to quantify the effect of these breakthroughs and other scenarios of interest to CMS and other policymakers. The model is flexible enough to consider life extensions and the interaction of treatment with disease, and it incorporates what is known about the health of future cohorts. Several key policy issues and recommendations arise as a result of this work.

Modeling Future Health and Spending

For our baseline scenario, we predicted the prevalence and Medicare costs for a particular disease in the next 30 years under the status quo (health status and disability trends defined by technology and risk factors of the elderly population in the 1990s). In this scenario, we held the health transitions and risk factors in the elderly population constant, so the variations in disease prevalence and costs came from only two sources: the health status of entering 65-year-olds and the population growth. Under the baseline scenario, Medicare expenditures will reach $360 billion in 2030.

We simulated the effects of medical breakthroughs and changes in risk factors on health status transitions (disease prevalence) and cost projections by altering the health status transition parameters or risk factors among the elderly according to the assessments from the expert panel. Thus, the difference in disease prevalence and costs between the base scenario and the breakthroughs scenario was solely attributable to the breakthroughs (e.g., eliminating heart disease among the entering 65-year-olds would result in a decrease in the prevalence of heart disease and total Medicare costs). But the mechanism is more complicated because of the interactions among all diseases, disability, and death in the health status transitions. In this case, eliminating heart disease among the young directly reduces costs, the risk of death, stroke, disability and nursing home residence; but the lower death rate results in an increase in the risk for other conditions and in life expectancy, both of which result in higher costs. The FEM explicitly models these interactions and provides estimates of the net effects. Thus, eliminating heart disease among the young would reduce heart disease prevalence by about 20 percentage points in 2030 and save Medicare $328 billion over the next 28 years. However, it also would increase the prevalence of cancer, stroke, diabetes, hypertension, lung disease, and arthritis; increase the prevalence of disability (ADL1+ and ADL3+); and have no significant effects on the prevalence of Alzheimer's disease and the use of nursing home care. The model can be used to quantify the future ramifications of changes in demographic trends and in patient behaviors and certain types of changes in medical technologies.

Implications of the Panel Findings

In Phase I, our TEPs identified the most important potential breakthroughs in four areas: cardiovascular disease, biology of aging and cancer, neurological disease, and health services. They provided estimates about the likelihood that a breakthrough could occur, the potential effect of the breakthrough, and the potential cost implications. Their work provides important insight into the future of medicine as it affects the elderly. Themes that emerged from the deliberations of the disease group panels included the following:

Improved disease prevention. Breakthroughs that improved prevention of disease were identified for all three disease categories. Nearly all the breakthroughs identified have relatively low per-person costs. However, because the interventions would need to be applied to very large populations, their cumulative costs are high. Counterbalancing these increased costs is the improvement in the direct cost of the care related to the prevented condition and improvements in morbidity and mortality.

Better detection or risk stratification of people with early disease. The health and expenditures of the future elderly could be dramatically affected by better detection of subclinical disease or early clinical disease, which will allow earlier and better targeting of effective therapies, to try to ameliorate the progression of morbidity and mortality associated with the diseases. Breakthroughs in this area were identified for cardiovascular diseases and by the health services panel. In both cases, the breakthroughs involve better detection of people at higher risk than the general population for worse outcomes from a variety of chronic conditions. The Human Genome Project is expected to vastly increase our ability to genotype people and determine their susceptibility to disease. Improved imaging should also increase our ability to detect subclinical disease.

Better treatment for patients with established disease. Breakthroughs in many different disciplines are likely to influence the treatment of established diseases:

- Advances in biomedical engineering were identified by the cardiovascular panel as being especially critical.
- Medical breakthroughs targeting genes or specific cells are also likely to have important consequences. All these breakthroughs tended to be of moderate cost, consistent with existing new drug therapies.
- Breakthroughs in cell or organ transplantation tend to be very expensive on a per-person basis and also face a host of ethical and technological challenges to successful implementation.

Breakthroughs identified by the health services panel included changes in the organization and delivery of health care that could improve the receipt of effective services; better care management; and changes in lifestyle, which could have the most dramatic consequences for the health and medical expenditures of the future elderly.

Implications of the Results of Our "What-If" Scenarios

As shown in the simulations of what-if scenarios, the existing FEM can be directly used to assess the future ramifications of changes in demographic trends (e.g., better-educated future elderly and rise in Hispanic population) and in patient behaviors (trends in risk factors, such as smoking and obesity) because these factors are explicitly built into the FEM as covariates in the hazard models.

For changes in medical technologies in the areas of primary prevention (e.g., technologies for disease immunization) and secondary prevention (e.g., screening tests), FEM can also be applied with only minor modifications. Examples include technologies that can eliminate heart disease among the young, a compound that extends life span, and diabetes prevention via insulin sensitization drugs.

For certain types of changes in medical technologies, moderate modifications need to be made to the FEM with detailed information on eligibility and the effect of these technologies on health status and costs. Examples include the development of telomerase inhibitors, cancer vaccines, and treatments for cardiovascular disease in the simulation scenarios.

For other types of changes in medical technologies and changes in the health care system, the existing FEM would need to be modified substantially. Examples include better care coordination, better medication management, and environmental improvements.

Our approach was broadly supported by our social science expert committee. The policy community generally has been interested in this approach as well, especially technical advisors to Medicare trustees, because of its great policy relevance: These potential breakthroughs could have important effects on future health conditions and health care expenditures, and the FEM could help CMS and other government agencies evaluate these effects as well as the effectiveness of corresponding policies. But FEM cannot replace the existing baseline forecasts developed by the CMS OACT and can only serve as a tool for evaluating specific trends or breakthroughs.

One limitation to our what-if scenarios that needs to be considered is that the panels did not adopt uniform definitions for likelihood of occurrence or adoption. The first panel had a difficult time assessing the likelihood of adoption, with estimates ranging in some cases from 0 to 100 percent. The reason for this range is that some interpreted "likelihood of adoption" as the likelihood that even one person would receive a treatment, whereas others interpreted the term to mean the likelihood that any eligible person would receive it (which would be close to the prevalence rate). After clarification of the term to refer to the likelihood of this procedure being an important part of clinical practice, subsequent panels estimated much less variable rates of adoption. Variation also existed in the definition of likelihood of occurrence (for a breakthrough). Technologies with a low probability of occurrence clearly would have been of less importance than those with higher probabilities. Thus, we did not consider the estimated likelihood of occurrence but rather the effect conditional on occurrence in our simulations.

Recommendations

Expand the expert panel process. Our expert panel process seems to have merit, but more assessment is needed. Ideally, this process would be made more formal and would be repeated at regular intervals. The choices made by this panel (and perhaps the alternatives they deem best) would be reviewed regularly. One alternative might include organizing panels by research areas, e.g., bioengineering or stem cells, rather than by disease type, so that experts can provide more detailed and reliable information about the breakthroughs in their areas of specialization. Key themes should be reviewed regularly. Scenarios would incorporate updated information and then make changes accordingly because of the rapidity of technological development.

Integrate the FEM into the OACT. The FEM is an innovative tool and produces interesting results that will be useful in several policy venues. The FEM is especially useful as a tool for conducting what-if simulations that explain what might happen with explicit changes in demographics and medical technology. It could be used by the OACT to answer questions about specific medical technologies. However, for it to be useful, the model needs to be kept up-to-date with recent MCBS and NHIS data.

Model complex scenarios. Some of the technologies identified in this report may have spillover effects, that is, therapeutic benefits in more than one area. For example, the use of a "longevity pill" that mimics caloric restriction might lower the risk of a number of diseases, in addition to extending life span. More information from the expert panels about joint probabilities and treatment scenarios would be useful. We relied on the literature review and the panel assessments to quantify these effects precisely; such quantification needs to be done on a case-by-case basis. Past assessment of novel technologies could also assist in this effort.

Model technology diffusion. The ultimate effect of a technology depends on its timing and its price, both of which are difficult to forecast, are interrelated, and influence its diffusion. But it is unclear how to forecast future prices in the context of our model. The panels recognized, but could not predict, that costs of a procedure will fall over time with higher rates of adoption: Costs are affected by both supply and demand factors.

Model recovery. Some of the health states in the MCBS, e.g. disability, nursing home entry, and possibly even some types of cancer, might allow for recovery. Recovery could be modeled in several ways. Since it is hard to predict who will recover, the easiest method is to examine the raw probabilities of leaving a health state in subsequent years, i.e., to assess the fraction of people who do not report a particular disease or functional state but who reported it in the previous year. This method is simply the reverse of the FEM health transitions model.

Collect additional information in the Medicare Current Beneficiary Survey. Our modeling exercise showed some of the unique benefits of the MCBS. The link between self-reported information and claims and enrollment information in Medicare is particularly useful. However, the MCBS has the disadvantage of containing poor economic data: in particular, employment, income, and wealth. Information on these economic factors would greatly improve the range of useful scenarios, since one could consider key economic trends. Furthermore, some self-reported information about disease and its treatment, e.g., whether people had angioplasty or

were taking oral hypoglycemics, would also allow much better links between claims data and self-reported information.

CHAPTER 1:
INTRODUCTION

To help the government take the actions necessary to keep the Medicare trust funds solvent, the Centers for Medicare & Medicaid Services (CMS) needs to generate accurate predictions of present and future health care spending. This process will require predicting how many people of various types will be alive in each future year and what their health care spending will be. The official projections of the aged beneficiary population by age and sex are currently taken from those of the Trustees' Reports of the Social Security Administration (SSA). These projections already take into account the long-term trends in decreasing age-specific mortality rates. The SSA population estimates make it clear that the baby boomers will greatly swell the ranks of the over-65 population starting in 2010.

Estimates of future health expenditures per person of a given age are more uncertain. Individual health care spending is a function of many factors: age, sex, health status, diseases and the medical technology to treat them, the price of care, insurance coverage, living arrangements, and care from family and friends. Estimates of spending per person are uncertain because they depend on hard-to-predict changes in all these factors. One can assume, as most actuarial models do, that the health status and spending for a given age-sex category will remain constant. In that case, estimated future Medicare expenditures are influenced only by changes in the age composition of the population, legislative changes such as those in the Balanced Budget Act of 1997, and general trends in spending that are applied uniformly across age-sex categories. But this approach—while straightforward—does not recognize key developments in demography, economics, and epidemiology that provide insight into future expenditures.

Most controversially, it appears that many people are staying healthy to older ages. As a consequence, morbidity, with its resulting functional limitations and costs, will be compressed into the last few years of life. Savings from compressed morbidity, however, may be offset by extended life expectancy. Current models do account for the added cost from reduced mortality. However, studies of particular diseases suggest that mortality gains have followed from lifestyle changes and primary and secondary disease prevention and from dramatically improved treatments. These same factors have also led to a postponement of disease, disability, and proximity to death, which are major predictors of higher expenditures. Thus, decreased mortality may have less effect on expenditures than current models that assume constant health by age would predict.

In response to these issues, the CMS contracted with RAND to develop models to project how changes in health status, disease, and disability among the next generation of elderly will affect future spending. The models allow us to conduct what-if scenarios, the exact nature of which were defined by national experts, to explore how various assumptions about the elderly and health care affect Medicare costs. We focus on two of the key determinants of spending: diseases (and the medical technology to treat them) and health status.

The primary objective of the study was to develop a demographic-economic model framework of health care spending projections that would enable CMS actuaries and

policymakers to ask and answer what-if questions about the effects of changes in health status on future health care costs. The model answers the following types of questions:

- What are the future health expenditures on Medicare likely to be during the next 25 years if the trends of the last decade are taken as projections into the next decade, and if disability among the elderly declines at a steady rate?

- How will the growth of future health care expenditures for the elderly be affected if advances in the development of new diagnostic tools, medical procedures, and new medications for chronic and fatal illnesses continue?

- How will the sociodemographic characteristics of the next generation of elderly individuals affect future health care spending?

The study was conducted in four phases:

During Phase I, we reviewed the current literature on trends in the health and functional status of the elderly, the likely effects of new medical advances and treatments on morbidity and mortality among the elderly, and the likely costs of new medical treatments. We also reviewed past efforts to model the effects of changes in health status, risk factors, and treatments on health care expenditures.

During Phase II, we convened technical expert panels (TEPs) to provide guidance on the likely future of advances in the medical treatment of specific illnesses and the early detection and prevention of diseases. Most of these panels consisted of physicians or biomedical researchers with expertise in the domains of cardiovascular disease, biology, cancer, neurology, or geriatrics. As part of Phase II, RAND also convened a separate expert panel, composed mainly of social scientists, to help us determine the appropriate health status measures, methodologies, and data sets for estimating model parameters, and the best modeling techniques.

During Phase III, we developed a demographic-economic model to project the probable health expenditures of the next generation of elderly. The model development was guided by the social science experts. Our future elderly model (FEM) is a microsimulation model that tracks elderly, Medicare-eligible individuals over time to project their health conditions, functional status, and ultimately their Medicare and total health care expenditures. It is based on the Medicare Current Beneficiary Survey (MCBS), a nationally representative sample of beneficiaries age 65 and older.

Finally, during Phase IV, we considered scenarios suggested by the experts—including potential breakthrough technologies as well as changes in lifestyle and the health care system—by exploring changes in the parameters of the model via what-if modeling. We considered several new technologies for treating heart disease, new treatments for cancer, and general changes in the sociodemographic status of the population.

CHAPTER 2:

PROSPECTS FOR MEDICAL ADVANCES IN THE 21ST CENTURY

The unprecedented progress in biomedical research over the final quarter of the last century will continue to drive a revolution in the practice of medicine. Every aspect of the prevention, diagnosis, treatment, and monitoring of disease processes has been affected by this revolution. In some cases, what appear to be trends in particular lines of research are not smooth progressions at all, but radical paradigm shifts. Behind this wave of advancement is a convergence of progress in many scientific fields, not simply the life sciences—anatomy, biochemistry, immunology, microbiology, physiology, pharmacology, and clinical medicine—but chemistry, physics, math, computer science, and engineering as well. Scientists from widely divergent disciplines are now crossing over to other disciplines or collaborating to form multidisciplinary teams of investigators to tackle problems of such technological magnitude that they could not have been approached within any one field. The pace of progress in some of these areas has no doubt been limited by the ability or the desire of scientists from heterogeneous research backgrounds to collaborate. Fortunately, policymakers and funding agencies have observed the trends, and funding of interdisciplinary research projects has begun to increase.

Based on the assessments of several groups of scientists and through literature reviews, this report outlines the technologies that are likely to have the greatest effect on medical practice and health care among the elderly in the first quarter of the 21st century. We begin with a discussion of the historical basis of each area, the scientific disciplines involved, the changes that will likely result, and the challenges that remain.

THE TECHNOLOGIES

Biomedical Engineering

Biomedical engineering is the application of multidisciplinary research that combines mechanical, electrical, computer, and chemical engineering with research in chemistry, physics, biology, physiology, and the other medical sciences. Over the next 25 years, it is expected that continuing advances in electronics, optics, materials, computer programming, and miniaturization will be applied to accelerate development of more sophisticated devices and techniques for basic research as well as diagnosis and therapy (Griffith and Grodzinsky, 2001).

Modern medical research is greatly indebted to biomedical engineering, a vast area that encompasses virtually all categories of technologies, each with a multitude of applications. What follows is a listing of many of these technologies, with a brief description of some of their applications. Many are discussed in further detail later in this chapter.

Molecular engineering. Molecular engineering is the application of physical and organic chemistry and chemical engineering as well as computer science to the identification and manipulation of living molecules. One of the most notable applications of molecular engineering has been the Human Genome Project, as described below. Other applications include the creation

of tailored monoclonal antibodies (antibodies raised in culture against specific antigenic components of protein molecules) and cytokines (factors that stimulate the proliferation of immune cells) for diagnosing and treating immune and other disorders, as well as elucidating the relationship between protein structure and biological function. Molecular engineering has also given rise to novel types of cancer therapy: assays to test novel drugs for rational drug design (see below), vectors for gene therapy (see below), and biomaterials to control cell proliferation and differentiation.

Cell and tissue engineering. Cell engineering is a well-established field that encompasses the development of devices, media, and other materials to optimize the proliferation of living cells in culture. Current applications include the large-scale manufacture of natural products with pharmacotherapeutic value such as peptide hormones and growth factors (discussed further below). Applications on the horizon include stem cell therapy (discussed further below), cell culture-based assays for diagnostics, and the development of new drugs and immune therapeutic techniques.

Tissue engineering, the large-scale growth of whole functioning tissues in culture, represents a natural progression from cell engineering. Ongoing for at least 15 years, current applications include epidermal tissue replacement for burn victims. Future applications will include regeneration and replacement of more complex tissues and organs as well as test systems for drug development.

Biomicroelectromechanical systems and microfluidics. Many biological processes of importance occur at the interface of a solid and a liquid or in a three-dimensional environment. In vitro systems that could mimic these environments have a variety of potential applications. For example, researchers use biomicroelectromechanical systems and microfluidics to create miniature environments in which cells are exposed to various concentrations of chemicals, shear forces, and/or crystalline surfaces. Such studies further our understanding of the processes involved in cellular homing and differentiation, immune response, cell proliferation, metastasis, and signal recognition and transmission. Similar systems can also be used to develop simple diagnostic tests and drug screening assays, to optimize cell culture environments, and to improve the ability of devices such as heart-lung machines to mimic their in vivo counterparts.

Virtual surgery, microsurgery, and micro-instrumentation. Advances in computer information storage and graphics capabilities and holographics are being applied to create simulations of invasive diagnostic and therapeutic procedures. These simulations are currently being developed for the purposes of undergraduate medical education, noninvasive training in surgery and diagnostics, and remote (tele-) diagnosis and surgery. Microsurgery applies advances in miniaturization, optics, and other aspects of instrumentation to minimally invasive surgery (see below).

Imaging. Advances in physics and chemistry as well as in computer programming are being applied to increase the resolution of existing diagnostic procedures and extend the range of diseases as well as normal processes that can be detected with minimal invasion (see below).

Bioinformatics. Progress in the elucidation of the human genetic code as well as in the elucidation of protein sequences and structure-function relationships that began well before (but

has been accelerated by) the inception of the Human Genome Project has given rise to increasingly vast quantities of biological information. The field of bioinformatics has evolved to develop tools to store, manage, and apply that information. Databases, algorithms, and computational tools must be designed to enable analysis and interpretation of these massive amounts of complex information.

Implications of the Human Genome Project

The Human Genome Project could give rise to an amazing number of medical breakthroughs. The immediate goal of this public-private venture is to decode every piece of DNA to learn the sequence of every gene in human chromosomes. The project also has a number of slightly less immediate goals. One such goal is to delineate noncoding sequences that play roles in controlling DNA replication (the process by which DNA is copied just prior to cell division) and transcription (the process by which DNA is read and messenger RNA is transcribed from it, the first step in protein synthesis). Another goal is to isolate and sequence genes associated with genetic disease states to determine the sites of mutation (Collins and McKusick, 2001).

Obtaining the sequence of the human genome will create vast opportunities to practice medicine in a more informed way. The most obvious, if not the most immediate, benefit of the project will be the identification of genes associated with diseases. Unfortunately, the diseases most prevalent among our increasingly aging population are not the simple one-gene diseases like hemophilia or cystic fibrosis. Diseases like cancer, type 2 diabetes mellitus, and cardiovascular disease are more than likely multigene diseases with the additional complexity of an environmental component to their etiology. Nevertheless, identification of at least the genetic components of chronic diseases will allow early risk assessment of individuals, which, in turn, will permit early preventive intervention. Researchers predict that by as early as 2010, predictive tests will be available for more than ten common conditions, including some types of cancer.

Elucidation of the human genome also will stimulate the design of new drugs. Such drugs may include genetically modified natural products and small molecules targeted at specific cells and cell-surface receptors. Possessing the sequence of the human genome will also allow researchers to predict responsiveness to drugs. As we discuss further below, advances in protein biochemistry as well as efficient, high-volume methods will be needed for the design, screening, and manufacture of small-molecule drugs. Forecasters expect that by 2020, the discipline of pharmacogenomics will commonly predict drug responses, and gene-based designer drugs will have been introduced for the treatment of cancer and other diseases.

Gene Therapy

Genetic modification of a patient's cells can alter gene expression for some therapeutic effects. Such modification may consist of inducing, increasing, turning off, or decreasing production of a gene product. This technology is already in the clinical trial phase of development.

Traditionally, gene therapy is used to treat hereditary disorders that are attributable to a defect in an identifiable gene by "replacement" of the defective gene with a normal copy of the

same gene. Alternatively, a normal copy of the gene may be introduced elsewhere in the genome where its expression can be controlled in a more or less normal manner. Clinical trials are currently being conducted on the use of gene therapy to treat several such diseases, including cystic fibrosis and hemophilia.

Another possible use of gene therapy includes genetic modification of cellular gene expression to treat diseases whose genetic bases are not straightforward or entirely understood. For example, the introduction of a gene whose protein product interrupts rapid cell division could be used to treat some types of cancer, even if the etiology of those cancers is unknown and may be unrelated to the product of the "foreign gene" (Kaji and Leiden, 2001). An alternative to introducing the gene for a protein product is to introduce a vector that makes "antisense DNA," that is, DNA complementary to the coding region of a gene for a protein of interest. Binding of antisense DNA to its gene complement prevents transcription of that gene. A gene for a protein that is believed to be involved in the growth or spread of the cancer would be a likely target. Such genetic modification might, in effect, be able to correct or compensate for the mutation(s) that caused the cancer. Examples include introduction of a vector that directs the synthesis of antisense DNA for a growth factor receptor believed to stimulate growth of a fast-growing type of brain tumor called an astrocytoma (Andrews et al., 2001).

Another application of genetic modification of cells will allow monitoring of the progress of cancer treatment, by introducing a gene for an easily traceable product (a marker) that would disappear when the cells stop dividing. Finally, gene therapy will ultimately permit the use of immunotherapeutic vaccines. By introducing (into a tumor) a gene the product of which is a cell surface antigen involved in recognition of foreign cells, the clinician will transform the tumor cells into a target for recognition and destruction by the immune system. To date, clinical trials have begun to test gene therapy treatments for a variety of diseases, including several types of cancer.

Thus far, three basic approaches to introducing new genes or genetic material are being tested. These approaches include the ex vivo approach, the in vivo approach, and the use of an encapsulation technique.

Ex vivo approaches involve removing a patient's own cells, allowing the cells to grow and divide in a culture system, introducing the genetic material of interest to the cultured cells (by a process called transformation), and reintroducing the cells to the patient. In lieu of the patient's own cells, cultured human cell lines can be transformed and introduced to the patient.

In vivo approaches involve the introduction of new or altered genes directly to the patient's body. Various methods are used (including direct inoculation) to ensure that the material reaches its target.

A third approach is to encapsulate genetically modified cells or genetic material. One example of an encapsulation device is the liposome, a synthetic vesicle surrounded by a lipid-soluble, bilayer membrane that is able to traverse cell membranes (Kaji and Leiden, 2001; Institute for the Future [IFF], 2000). The use of liposomes eliminates the need for viral vectors.

In addition to the requirement for a healthy gene or some other nucleic acid of interest, the gene therapy process requires two other components. These components consist of a vector to deliver the genetic material and some mechanism by which to introduce the gene-containing vector to the target cells.

Vectors must be easy to produce or reproduce. In addition, they must be capable of transforming nonproliferating (nondividing) cells efficiently, since the majority of noncancerous tissues and organs in the body consist of such nonproliferating cells. Finally, the vector must be capable of irreversibly introducing the DNA of interest into the recipient cells' genome without causing illness or an immune response. Simple plasmids, small self-replicating circular pieces of DNA that carry the genomes of single-celled organisms, are easy to produce but do not transform nonproliferating cells efficiently. Moreover, they can cause immune reactions in their recipients. Currently, the vectors most frequently used are the genomes of rodent retroviruses (viruses the genome of which is RNA rather than DNA based) that have been inactivated (disabled) to prevent their causing viral illnesses (IFF, 2000). These vectors appear to work well in targeting proliferating (rapidly dividing) cells, an advantage when the target tissue is a tumor or other cancerous cells. However, they do not work well in targeting non-proliferating cells, which are the usual target of interest for traditional gene therapy. Vectors made from the genome of inactivated adenovirus, a mammalian DNA virus, transform non-proliferating cells efficiently but cause local and systemic immune responses. Problems with vector development appear likely to limit progress in gene therapy for some time (Kaji and Leiden, 2001). One alternative that is being tested and appears to show safety and efficacy in Phase 1 trials is the transformation of fibroblasts, a rapidly proliferating and relatively undifferentiated type of cell that is taken from the patient's own skin. The transformed fibroblasts are allowed to proliferate in culture before reintroduction into the patient.

Devices to introduce the vector-gene combinations or transformed cells into the target cells of interest present a further challenge. The catheters used to deliver the genetic material or cells have tended to inactivate viral vectors. Thus, considerable research is needed to optimize delivery devices.

Some concern has also been raised about the possibility that the introduction of foreign genetic material in the form of viral vectors might modify the genetic composition of "germ line" cells, that is, egg cells and the cells that give rise to sperm. Thus, some vector DNA could be passed onto a patient's offspring. Better methods of targeting as well as greater understanding of the processes by which vector DNA is taken up and handled should eventually alleviate this concern.

Stem Cell Therapy

Stem cells are undifferentiated, totipotent cells that are the precursors to all other cells in the body. The conditions required for commitment of undifferentiated stem cells to some particular destination (both physical and in terms of cell type) as well as the processes involved have been the subject of intensive research efforts for more than a century and are just now beginning to be understood. Stem cell therapy takes advantage of the totipotency of these cells by transplanting the cells to a recipient for the purpose of regenerating or replacing damaged or aging tissue.

Several recent advances have fueled researchers' attempts to use stem cells for tissue replacement. These advances represent the convergence of progress in a number of different areas of biology and clinical medicine.

First, the undifferentiated cells have been found in organs and tissues that were previously thought to contain only terminally differentiated cells. Moreover, conditions for growing such cells in culture as well as allowing them to divide and differentiate have been developed, as have techniques for transplanting these tissues into target organs.

Second, researchers have found that the stem cells isolated from particular organs and tissue types retain greater totipotency or plasticity than previously thought. For example, as researchers recently announced, stem cells found in adipose tissue can be made to differentiate to other types of tissue.

Finally, as news stories have been reporting for approximately a decade, stem cells isolated from human embryos early in development can be induced to differentiate both in cell culture and after transplant to human recipients (Kaji and Leiden, 2001). Studies are already underway to test the ability of such embryonic or fetal stem cells to replace human tissue damaged by disease. The most well-known example of this line of research is probably the implantation of embryonic stem cells into the brains of patients with Parkinson's disease in an effort to regenerate the neurons that control intentional movement.

Pharmacotherapeutics: The influence of advances in basic sciences on pharmaceutical research. Recent advances in pharmacotherapeutics take advantage of novel biomedical research, particularly the Human Genome Project. Pharmacologists are now engaging in "rational drug design" (IFF, 2000), which incorporates knowledge of the physical and molecular structure of a drug's cellular target into the design of the optimal drug. In the past, new drugs often were discovered serendipitously or by tinkering with the chemical structures of existing agents. The first priority of new drug design now is to identify control points in the physiological pathways involved in disease processes as potential targets for drug effects.

Among the advances contributing to rational drug design is the revelation of the sequence of the human genome. Identifying DNA sequences of genes will simplify learning the amino acid sequence of vast numbers of proteins (Bumol and Watanabe, 2001). Moreover, the techniques of genetic engineering and scale-up (batch) cell culture now permit the synthesis of infinite variations of novel proteins and large-scale production of enough of each to conduct initial testing.

Knowledge of the amino acid sequences of more proteins as well as advances in the chemistry and physics of three-dimensional structural elucidation and computer modeling are permitting identification of structure-function relationships in proteins and their interactions with other molecules. Understanding these kinds of relationships, such as the three-dimensional interaction of a peptide neurotransmitter with its polypeptide receptor, allows structure-based design of drugs (for example, the design of a drug that interacts with only a certain class of dopamine receptors).

Finally, the Human Genome Project will permit elucidation of the pathways involved in specific disease processes via a technique called transcript profiling. Transcript profiling enables the identification of genes the expression of which changes during disease processes and that thus have the potential to become candidate targets for drugs.

Several types of molecules are likely to emerge as candidates for new drugs. These molecules include recombinant proteins, monoclonal antibodies, peptides, and small organic molecules. Recombinant proteins are those proteins synthesized by transforming cultured cells or entire organisms. The use of genetic engineering techniques now permits large-scale in vitro production of pharmacotherapeutic proteins such as human insulin and growth hormone as well as clotting factors, obviating the need to purify these hormones from animal sources or from potentially contaminated human blood.

Monoclonal antibodies are antibodies raised in vitro against a single specific site on a protein molecule. In addition to their uses in the research lab for elucidating structure-function relationships within proteins and protein-protein interactions, monoclonal antibodies will be the next class of vaccines.

Peptides (short chains of ten or fewer amino acids) and small synthetic organic molecules are easy to synthesize in multiple combinations. These agents are expected to be able to target active sites of proteins and cell surface receptors as they are revealed.

Biomedical Imaging

Imaging techniques use physical devices to detect the unique chemical and physical properties of internal structures—tissues and organ systems—or some subset of their functions, for the purpose of visualization. Such techniques expand the capabilities of noninvasive diagnosis and localization, reducing the need for invasive procedures. Diagnostic imaging is not a new technique: X-rays have been used to visualize solid internal structures for 100 years. Moreover, computerized tomographic (CT) scanning, as well as magnetic resonance imaging (MRI), positive emission tomography (PET), and ultrasonography are no longer even new techniques. However, recent advances in physics, chemistry, materials engineering, and imaging as well as in other biomedical fields portend dramatic progress in the use of biomedical imaging (BMI). BMI may now be applied not only to diagnose and monitor the progress of treatment for many conditions but also to perform basic research on the causes of those conditions.

The imaging process consists of four basic components, each of which may be affected by changes in technology (IFF, 2000).

The first component consists of emission of energy from some source. The type, source, and amount of energy determine what can be detected. A trade-off exists between increasing power for greater or more precise detection and the potential for tissue damage. For example, the use of greater amounts of X-irradiation to increase the capability of mammography to detect small tumor foci or to penetrate dense breast tissue may increase the risk of inducing a cancerous lesion. Research on focus of beams as well as alternate sources of energy is ongoing and has already led to potentially new diagnostic methods for breast cancer, prostate cancer, and Alzheimer's disease.

The second component is detection, by a receiver, of the energy that emerges from the tissue (in the case of X-ray, CT, or ultrasound) or the change in the state of the tissue as a result of the application of some energy (in the case of MRI). Advances in computerization have been applied to the creation of increasingly sensitive detectors, for example, full-field digital mammography employs electronic sensors to capture the X-ray image and send the data to a computer (Patlak, et al., 2001). Trends in microelectronics toward increasing miniaturization are expected to drive creation of smaller receivers that will have the advantage of portability, if not lower cost. Advances in contrast media that will highlight changes at the organ, tissue, and cellular (as well as reaction) level are ongoing.

The third component is analysis of the raw data that result from detection of the output. Increases in computer capacity as well as in development of algorithms and analytic techniques are expected to lead to advances in pattern detection in visual images.

The fourth and final component of the imaging process is the display; the transformation of the analyzed data to a visual image, such as a radiograph, a set of CT scans, or the visual display of ultrasound images. Recent developments in electronic engineering will soon result in larger, more detailed images in a shorter time and at less cost than traditional display methods.

The most intriguing of the recent breakthroughs (in all four areas) have enabled visualization of various tissue properties, such as the occurrence of cell division and changes in the uptake of molecules, such as metabolic fuels. These advances will expand the potential research and diagnostic applications. For example, more powerful computer processing has decreased the time required for MRI imaging and overcome the interference of movement, enabling MRI to be applied to the heart and other organ systems as well as the fetus.

According to IFF (2000), three major areas of research are likely to take advantage of the progress in BMI combined with the results of the Human Genome Project to produce changes in how diseases are detected and treated. Advances in the application of techniques for identification of molecules and their energy states will lead to new techniques for visualizing physiological and pathophysiological subcellular processes (such as cell division and neurotransmitter release and reuptake). Advances in optics and miniaturization as well as computerization and display technologies will assist in the development of image-guided therapy and assessment of treatment progress. Finally, progress in the application of bioinformatics to analysis of imaging output data will permit greater resolution.

New techniques for imaging subcellular processes. Advances in several existing techniques as well as the application of developing technologies are expanding the capabilities of PET, single photon emission computed tomography (SPECT), and other types of imaging. The use of electron beam CT scanning permits faster scanning and image processing than does conventional CT (IFF, 2000). A new ultrasound technique, harmonic imaging, uses a receiver that is tuned to a higher frequency than that used for conventional ultrasound. The resulting improvement in image resolution can overcome barriers provided by certain body types and conditions to the use of conventional ultrasound.

PET and SPECT allow direct imaging of subcellular functions such as cellular uptake of molecules, enzymatic reactions, and the release and action of neurotransmitters. Use of these

techniques has permitted the visualization of altered brain function in particular emotional states, during problem solving, and in some disease states, and may soon allow early diagnosis and monitoring of the progress of neurological diseases.

MRI has been applied to the visualization and diagnosis of physical changes to soft tissues. An advancement, diffusion weighted MRI, will allow distinction between healthy tissue and areas affected by disease processes such as stroke and edema. MR spectroscopy measures metabolic differences between tissue areas, thus allowing detection of focal tumor development. This technique has already proven useful for staging and monitoring treatment of prostate cancer. The current challenge facing researchers is to improve the ability to perform imaging of in vivo molecular and cellular events in real time. Advances in the technology of magnets and MR surface coils as well as multimodal imaging devices (those that employ more than one type of imaging simultaneously) will allow improved three-dimensional image resolution as well as visualization of changes over time.

Image-guided therapy: The ultimate application. The application of imaging techniques to therapeutics is actually a multidisciplinary field that requires the expertise of anatomists, physiologists, chemists, physicists, engineers, computer scientists, bioinformaticians, pharmacologists, and clinicians of many specialties. Imaging systems can simplify a variety of surgical procedures, often involving lesions that could not otherwise be detected. Functional imaging such as that described above allows surgeons to monitor tissue or behavioral functioning during a procedure. In addition, clinicians are beginning to rely on imaging to monitor the progress of treatment via molecular or biochemical pathways. The challenge that image-guided therapy and treatment monitoring currently poses to researchers and clinicians involves the need for new methods to visualize treatment effects. Such effects include apoptosis (cell death), the disappearance of malignant cells, and the growth or disappearance of blood vessels.

The outlook for imaging in the near future. The greatest efforts in the near future are likely to be applied to refinement of optical imaging techniques (as well as PET and MRI) that permit visualization of changes at the level of individual biochemical reactions. Advances are also expected in the area of image-guided therapy. Modifications of existing techniques will expand their utility; for example, the use of open MR will permit the advancement of MR-guided surgery, while improvements in image integration and resolution will increase the effectiveness of image-guided diagnosis and treatment (Tempany and McNeil, 2001). The results of the Human Genome Project are likely to be combined with BMI techniques for the purpose of risk assessment and reduction.

Some studies suggest that the optimal use of imaging for screening and diagnosis may involve combinations of several technologies. For example, a recent Institute of Medicine (IOM) report (Committee on Technologies for the Early Detection of Breast Cancer, et al., 2001) concluded that no single type of imaging can detect all breast cancers. While some of the newer imaging technologies show promise for the detection of breast cancers, further research is needed, and film mammography remains the reference standard for breast cancer detection. The authors suggested that ultrasound and MRI may be useful adjuncts to mammography for the diagnosis of breast cancer.

According to Tempany and McNeil (2001), the area in which progress is most needed is the cross-disciplinary application of the technique itself to the needs of patients. Because the various disciplines that have contributed to the progress of BMI have not collaborated in the past, efforts will need to be made to bring them together. Such collaboration may be most effectively encouraged at the training level (in medical and graduate schools) through interdisciplinary training fellowships and coursework. A related challenge is to update the curricula for training radiologists in the skills needed for the newer diagnostic modalities.

Minimally Invasive Surgery

According to Mack (2001) advances in surgical techniques during the last 25 years have brought about a major paradigm shift in the methodology used to perform at least some surgical procedures. For these procedures, surgeons no longer directly touch or see the structures on which they are performing surgery. Instead, the organs or tissues are visualized using tiny scopes that have been introduced through existing orifices or small incisions, and the surgical procedures themselves are performed with miniature hand-held or robot-directed instruments. These trends toward surgery that is minimally invasive and robotically performed are improving the outcome of surgical procedures while decreasing complications, hospital stays, recovery time, and costs. Driving these advances in minimally invasive surgery is the fact that in most types of surgery, the morbidity that results is largely the result of the procedures required to gain access to the affected area, rather than the procedure that is finally performed on the target organ.

The technological advances that have made minimally invasive or endoscopic surgery possible are numerous. Advances in video imaging (via development of the charge-coupling device chip), image digitization, and development of high-intensity light sources, including advances in fiber-optic technology have all contributed to improvements in visualization. In addition, developments in miniaturization and improvements in hand instrumentation as well as navigational systems for vascular catheters have helped optimize performance of the procedures themselves (Mack, 2001; IFF, 2000).

The most well-known applications of endoscopic surgery to date are gall bladder excision, sinus surgery, transvaginal hysterectomy (and other pelvic procedures), and arthroscopic joint surgery. However, thus far, these advances have not spread to many other types of surgery.

Surgical procedures are divided into three categories: excisional (surgical removal of part or all of a structure), ablative (destruction of a structure, usually with locally applied heat), and reconstructive (repair or replacement of a structure). Of the three types of surgery, only excisional and ablative surgery lend themselves well to endoscopy, because of the greater need for open, three-dimensional space and the frequent need to introduce new tissue for reconstruction procedures.

Similarly, frequently performed (high-volume) procedures lend themselves to endoscopy better than do rare (low-volume) procedures because of the need to perfect the techniques; surgeons have a greater opportunity to learn and perfect high-volume procedures. However, many high-volume procedures, such as coronary artery bypass grafting, do not lend themselves well to endoscopy, because of their complex, reconstructive nature (Mack, 2001). Nevertheless,

the technology is currently being applied to image-guided brain surgery and many types of endovascular reconstructive surgery, including the placement of endovascular grafts for abdominal (and brain) aneurysms. In addition, endoscopic procedures are used to perform fine-needle biopsy for non-invasive diagnosis (IFF, 2000).

Some progress has been made in moving toward minimally invasive cardiac surgery. In contrast to surgical procedures in which the majority of morbidity is associated with the incisions required to gain access, the morbidity that results from traditional cardiac surgery is greater than that associated with the sternotomy itself. According to Mack, several approaches have been used to decrease the invasiveness of cardiac surgery. Off-pump coronary artery bypass grafting, the most current procedure, is performed through a traditional incision, under direct vision and with conventional surgical instruments. However, the heart-lung machine has been eliminated, and the procedure is performed on a beating heart (mechanical stabilizers are used to stabilize the coronary artery to be bypassed), which improves surgical outcomes. This technique, which is being used in about 20 percent of all bypasses, is still in development.

Current efforts focus on developing minimally invasive approaches to more complex traditional procedures. For example, hand-assisted laparoscopy will allow endoscopic approaches to be applied to procedures that are now performed in a completely open surgical environment. Another advancement is the use of implantable devices to treat conditions such as gastroesophageal refluxing disease. The use of biochemical sealants in place of sutures and staples is decreasing the invasiveness of some procedures. Finally, as is discussed below, robotic techniques are being perfected to increase the precision of traditional open surgical procedures.

Robotics and other remote surgical techniques. Robotics originally evolved as a means for conducting procedures at a remote site, such as a battlefield or space station. For a variety of reasons, this application of robotics has not taken hold in health care, although the concept of telemedicine, whereby experienced surgeons provide guidance to practitioners at remote locations via a video screen, seems to have taken its place. However, robotics may be applied to minimally invasive surgical techniques in cases where it can increase "manual" dexterity and assist in image-guided therapy. For example, robotics should soon allow fine procedures such as retinal vein cannulation (for administration of local therapy) that cannot currently be performed manually. Robotics and telemedicine can also be used to simulate surgical environments for didactic purposes.

Endoscopic surgery presents several barriers that may be surmountable with advanced robotics. For example, the use of two-dimensional imaging to visualize three-dimensional spaces results in loss of resolution, and current three-dimensional technologies suffer from limited image resolution. However, the most significant barrier may be the limited space for movement. Current research is applying computer and robotic assistance approaches to overcome these obstacles. It is expected that in the near future, three-dimensional MRI will be used to increase image resolution (Mack, 2001). Interventional MRI also will be used to expand the scope of procedures (IFF, 2000).

Future efforts. Current and future efforts are expected to focus on procedures that can be performed through naturally occurring orifices. Other developments will include procedures for image-guided remote delivery of focused energy for ablative treatment (such as ultrasound or

radiation). Breakthroughs in miniaturization, as well as chip and wireless technology will pave the way for cameras that can be swallowed as well as implantable sensors (to detect physiological changes such as altered electrolyte levels or cell division activity), information storage devices, robots, and other implants that can be externally controlled (Mack, 2001). Interventional MRI (and minimally invasive procedures) will change the way acute stroke is treated over the next 25 years. Pharmacological advances and the rapid transfer of stroke and other vascular accident victims to nearby vascular facilities will allow physicians to diagnose and treat these patients quickly and minimize damage. Minimally invasive procedures are already shortening hospital stays and increasing the number of procedures that can be performed in ambulatory settings, resulting in lower costs (IFF, 2000).

One of the greatest challenges wrought by the new technologies is an educational one. Medical students must become increasingly proficient in the physical and mathematical sciences both to understand and to take advantage of the potential of these new techniques. Furthermore, experienced surgeons now must seek postgraduate training to become proficient in minimally invasive surgical procedures or risk becoming obsolete.

Organ and Tissue Replacement and Xenotransplantation

Organ failure and tissue loss account for a high percentage of health care costs today, particularly among older adults. Thus, this percentage is expected to rise as the average age of the population increases. Current treatments include transplantation, surgical reconstruction, and mechanical devices such as kidney dialysis machines, each with its own limitations. Of the three methods, transplantation of organs and tissues has the greatest potential, not only to treat gross organ failure (such as renal failure), but also to treat chronic conditions like diabetes and Parkinson's disease, congenital conditions such as hemophilia, and acquired conditions such as cancer.

However, the limitations of organ transplantation include a shortage of organs, damage to donor organs during the transport process, and rejection of immunologically incompatible organs and tissues. Tens of thousands of patients await donor organs (Niklason and Langer, 2001).

Current research efforts can be divided into five areas. The first area includes methods for improving organ preservation during transport from donor to recipient. A second area includes procedures for lengthening postimplantation survival of the organ and the recipient. A third area includes xenotransplantation (the transplantation of cells, tissues, and whole organs across species). A fourth area consists of improvement in devices to replace organs or organ function. Finally, alternative strategies are being used to develop new organs, taking advantage of advances already described above in stem cell biology, genetic engineering, and tissue engineering. Several of these areas are discussed briefly below.

Lengthening post-transplant organ survival. A variety of techniques are being examined to prevent injury that results from temporary ischemia and reperfusion of the transplanted organ. Another area of research already mentioned and discussed further below is that of preventing rejection of the donor organ or tissue using a variety of tissue and molecular manipulations.

Xenotransplantation. Current xenotransplantation research focuses on the pig as organ donor because of its size and commonalities with humans in some physiological pathways. Not surprisingly, rejection is a more significant issue with xenotransplantation than with intraspecies transplantation. New strategies are being examined for their ability to prevent rejection of organ allografts. The goal of preventing rejection of donor tissue is to suppress selectively the immune response to the organ while retaining normal immune response to pathogens. Techniques to accomplish this selective immune suppression are expected to improve in the future as researchers gain and apply new knowledge about immune function from the results of the Human Genome Project. A number of potential methods are under consideration and are currently being pursued. These include transplantation of bone marrow (as a source of precursor donor T cells) along with an organ, clonal T-cell deletion, as well as modification of the donor to increase its compatibility with the recipient (Niklason and Langer, 2001; IFF, 2000). The latter is considered to be the more likely to demonstrate success, with transgenic techniques being used to introduce genes for recipient surface antigens.

A number of additional issues must be overcome before xenotransplantation becomes widespread. For example, organs and tissues from animal sources may carry endogenous retroviruses, which must be identified and removed. Nevertheless, xenotransplants of nervous tissue are currently being used to treat patients with Parkinson's disease (IFF, 2000).

Alternative strategies for developing organ and tissue replacements. Engineering of replacement tissues is now possible via large-scale tissue culture. However, further work is necessary to extend our current cell and tissue culture techniques, which are relatively crude, and to determine the conditions required to create organ systems in vitro (for example, further knowledge is needed about matrices and factors that control tissue architecture). Use of undifferentiated pluripotent stem cells (and other undifferentiated cells) will extend the possibilities for tissue culture. Further research is needed on stem cell isolation and culture. Identification of cell surface markers will allow easier isolation of stem cells. In addition, the conditions required for stem cell differentiation must be identified. These include signaling pathways, transcription factors, and gene activation sequences (Niklason and Langer, 2001).

Artificial Blood

Blood transfusions are used to replace lost volume and to increase the capacity to carry oxygen. However, lost volume can be replaced with a number of synthetic substances, such as colloidal suspensions. Traditionally, research aimed at developing an artificial blood product has been limited to the military. However, because of the periodic shortage of blood and the concern about transmission of infections through blood transfusions that increased through the late 1980s and early 1990s (prior to routine, reliable screening of blood), interest in developing artificial blood has increased (IFF, 2000). Artificial blood should be ready for release within the first five years of the 21st century (Cimons, 2001). Artificial blood has the advantages of having a longer shelf life than natural blood as well as safety and universal compatibility across all blood types.

Hemoglobin-free artificial blood products have been approved by the U.S. Food and Drug Administration (FDA) but do not permit optimal tissue oxygenation. Until recently, hemoglobin-containing products relied on bovine hemoglobin, which causes kidney damage, and outdated

blood, which may pose several health risks. Thus, creation of a safe product that supports tissue oxygenation awaits cloning and mass-production of recombinant human hemoglobin.

Using genetic engineering, a U.S. company has manufactured recombinant human hemoglobin that is handled identically to human hemoglobin by the human kidney. The remaining drawback to the artificial blood products now in development is that they cannot perform all the functions of blood, for example, they cannot fight infection (IFF, 2000).

The next three chapters summarize the methods and results of a series of evidence-based analyses of breakthroughs in technology that have the potential to influence the prevention, diagnosis, treatment, and monitoring of disease conditions. These analyses are organized by system or category of disease, rather than by technology, and were identified by leading experts as described in Chapter 3.

CHAPTER 3:

THE MEDICAL EXPERT PANELS

In some lines of research, trends that appear from a distance to be smooth progressions are in fact radical paradigm shifts. Behind this wave of advancement is a convergence of progress in many scientific fields, including anatomy, biochemistry, immunology, microbiology, physiology, pharmacology, health services, and clinical medicine as well as chemistry, physics, math, computer science, and engineering. Scientists from widely divergent disciplines are now crossing over to other disciplines or collaborating to form multidisciplinary teams of investigators to tackle problems of such magnitude that they could not have been approached within any one field.

Keeping up with the rapidity of change is difficult enough: Predicting its possible course may be foolhardy. Nonetheless, because new technologies of all types are the driving force behind changes in both quality and cost of care, we accepted the dual challenge of developing a method to predict the effect of new technologies on health care for the elderly in the next 10 and 20 years and then applying that method to do so. It is hoped that the results of our analyses will help us make more rational health policies as we cope with questions ranging from, Will we be able to afford the new care? to What personnel will be needed to provide it?

Previous attempts to assess potential future technologies have relied on one or, at most, a few experts, whose opinions were gathered and assessed in an informal manner. We developed a quantitative method to assess the likelihood and effect of potential medical breakthroughs that combines lessons learned from evidence-based medicine on conducting literature reviews and "horizon scanning" with focused expert judgment collected using a combination of informal and formal methods. The process is described here briefly. For a more detailed description, refer to Appendixes A and B.

THE PROCESS

We began by convening a panel of six leading geriatricians and asking them to identify those clinical domains where potential breakthroughs would have the largest effect in terms of costs and health status. This group selected cardiovascular disease, the biology of aging and cancer, neurological disease, and changes in health care services as the most important clinical domains.

Within each domain are several important conditions. For example, neurological disease encompasses Alzheimer's disease, Parkinson's disease, and general cognitive impairment. Cardiovascular disease (CVD) encompasses coronary artery disease (CAD), heart failure (HF), and disturbances of cardiac rhythm. The domain of "cancer" was combined with "aging" because the two are fundamentally related at the biological level: Many normal cells have programmed senescence, and cancer cells must escape this destiny to become malignant. Thus, studies of the biology of cancer have informed the biology of aging and vice versa. A deeper understanding of the biology of aging has the potential to affect not just the diagnosis and treatment of cancer, but all of the disorders characteristic of older age, including dementia, vascular disease, and functional decline.

Selection of the Medical Technical Expert Panels

Groups of technical experts were then selected for each of the three topic areas. We sought individuals who represented a broad range of expertise, including clinicians and basic scientists. To select the technical experts, we used our past experience with similar expert panels, the published literature, and the advice of local experts and experts at the sponsoring institution, the Centers for Medicare & Medicaid Services (see Appendix Tables C.1–C.3 for names and affiliations).

Selection of the Potential Medical Breakthroughs for Further Evaluation

The technical experts were surveyed individually for their opinions regarding the leading potential medical breakthroughs in each area. In making these decisions, they were asked to consider the likelihood that a breakthrough could occur, the potential effect of the breakthrough, and the potential cost implications. We then collated the responses, and combined those areas named most frequently by the experts with the results of preliminary "horizon scanning" literature searches to select potential breakthroughs for further review.

Full Literature Search

For each of the selected potential medical breakthroughs in cardiovascular disease, the biology of aging and cancer, and neurological disease, we next conducted a comprehensive literature search. We searched traditional databases such as Medline, Healthstar, and Embase as well as the Pharmaceutical News Index, International Pharmaceutical Abstracts, Current Biotech Abstracts, Drug News and Perspectives, ESPICOM Pharm and Med News Device, FDC Reports, Ads, Newsletters, and relevant biotechnology abstracts. The details of each search are in Appendix Tables D.1–D.3.

Article Selection

Titles and abstracts were reviewed by one of two physician investigators trained in literature searching and review, evidence-based medicine, and health services research. A sample of titles that was subjected to dual independent review revealed greater than 90 percent concordance between the two physician reviewers. We selected articles for further evaluation if they reported evidence regarding the actual or potential beneficial outcomes that could accrue from a specific intervention or if they described recent or potential future advances in a topic area or intervention. In this regard, we found that recent relevant review articles or articles describing new advances were most useful.

Panel Meeting

Each of the three medical technical expert panels met for one day to discuss the potential breakthroughs. We used a combination of the nominal group process to list and define potential breakthroughs for further discussion, the informal group process to discuss the evidence and opinion regarding each topic, and formal voting to develop specific estimates for the following four subjects (Table 3.1):

1. The target population to whom the breakthrough would apply
2. The likelihood of the breakthrough occurring in the next 10 years and the next 20 years
3. Expected effect on morbidity and mortality of the breakthrough
4. Expected cost of the breakthrough.

The nominal group process involved, first, presenting to the group the preliminary list of breakthroughs, and then asking each panelist whether he or she wished to add any breakthroughs to the list. After this solicitation, the group discussed the relative merits of the breakthroughs and then selected the final list.

The formal voting involved collecting from each panelist his or her estimate of the likelihood of the breakthrough occurring and the potential effect on morbidity and mortality. The process generated a range of probabilities in order to quantify uncertainty about the forecasts of breakthroughs. Since costs of the breakthrough can be particularly difficult to estimate, in some cases the panelists identified an existing technology they thought would be similar in cost to the new technology when it was fully implemented.

The following sections describe the results of the panel process for each category of diseases.

CARDIOVASCULAR DISEASES

Based on the results of the nominal group process, the original list of eight potential breakthroughs was modified and expanded to the following ten topics, which were then discussed in more detail.

- **Improved prevention of disease**

  This could occur through improved uptake of what we already know to be effective (normalizing weight, control of blood pressure and diabetes, lowering cholesterol, etc.) or through as yet unknown pharmaceuticals such as an anti-obesity drug, a cure for diabetes, or a cure for cholesterol.

- **Noninvasive diagnostic imaging to improve risk stratification**

  Candidates for breakthroughs in noninvasive diagnostic imaging (NDI) included electron-beam computerized tomography scanning, magnetic resonance, ultrasound to assess intimal thickness, and a new method to assess the vulnerability of plaques to rupture. All of these represent methods to visualize all or part of the coronary artery or plaques therein without requiring invasive angiography.

- **Magnetic resonance angiography as a replacement for coronary catheterization**

  Magnetic resonance imaging technology is widely used for static images of soft tissues in the body. Adapting this technology to the dynamic movement of the heart and increasing

resolution such that plaques within coronary arteries can be visualized represent major conceptual challenges. This topic considers whether those challenges can be overcome.

- **Intraventricular cardioverter defibrillators**

  Intraventricular cardioverter defibrillators are devices implanted in the heart that continuously monitor the heart rhythm and apply a therapeutic shock when ventricular tachycardia or ventricular fibrillation is detected. This is an existing technology that recent clinical trials have shown to be beneficial in new clinical indications. If the results of ongoing clinical trials are positive, they have the potential to greatly expand the indications for these expensive devices.

- **Left ventricular assist devices (LVAD)**

  These devices, which, in some sense, are "artificial hearts," are implanted into the thorax and aid the left ventricle of the heart in pumping blood. This is a technology that currently exists as a bridge to transplant, but improvements in the devices may allow permanent implantation.

- **Xenotransplants**

  If the current difficulties surrounding the use of pig hearts in humans could be overcome, the use of such transplants could expand greatly.

- **Therapeutic angiogenesis**

  Therapeutic angiogenesis involves the injection into the heart muscle of human growth factors that stimulate the development of new blood vessels. This technology is currently undergoing clinical trials in humans. Possible uses are as a replacement for conventional revascularization or as an augmentation to revascularization.

- **Transmyocardial Revascularization**

  Transmyocardial revascularization (TMR) is a technique in which holes are punched in the heart muscle to stimulate growth of new blood vessels.

- **Control of atrial fibrillation**

  Atrial fibrillation is a disturbance of the heart rhythm that is common in older persons and contributes to both HF and stroke. Three candidates for improved control were considered here: new generations of pacemaker/defibrillators, catheter-based ablation techniques (use of a catheter to interrupt the pathways by which disordered electrical currents are maintained), and new drugs. In terms of effect, drugs were considered to be unlikely to be a breakthrough; therefore, we did not discuss them further.

- **Pacemaker/defibrillators**

- **Catheter-based ablation techniques**

The results of the group process for each potential breakthrough in the treatment of cardiovascular diseases are depicted in Table 3.1. The first panel had a difficult time assessing the likelihood of occurrence (adoption): In many instances, their estimates ranged from 0 percent to 100 percent. In part, this tremendous variation may have been the result of some confusion over the meaning of these probabilities. Some panel members may have interpreted it to be the probability that at least one person will be treated using this method in the future, whereas others may have interpreted it as the likelihood that any eligible person would receive this type of treatment, which is much closer to a prevalence rate. When this issue was clarified for future panels, the probability ranges were much smaller.

Table 3.1. Summary Results of Cardiovascular Diseases Medical Technical Expert Panel

Improved prevention of disease

Eligible population	The general population >45
Likelihood of occurrence by 10 years (%)	20 (range 10–100)
Likelihood of occurrence by 20 years (%)	40 (range 15–100)
Effect	Similar to that reported in Stanler et al. (1999) for the relative risk in CVD in patients with favorable values for the 3 main coronary risk factors. This paper reported age-adjusted relative risk of CHD mortality of 0.08 to 0.23; and estimated greater life expectancy 5.8 to 9.5 years.
Cost	Presumably low, on the order of what existing medicines for lipid control cost today. Average wholesale price (AWP) for Atorvastatin $209.88 for 30-day treatment at 80 mg/day AWP for Pravastatin $106.77 for 30-day treatment at 40 mg/day AWP for Cerivastatin $39.60 for 30-day treatment at 0.3 mg/day

Noninvasive diagnostic imaging to improve risk stratification[a]

Eligible population	General population>45	Subclinical disease: Risk factors for CAD or HF meaning ICD-9 diagnosis of hypertension, diabetes, etc.	Clinical disease: Established CAD or HF
Likelihood of occurrence by 10 years (%)	10 (range 5–25)	75 (range 10–75)	50 (range 10–75)
Likelihood of occurrence by 20 years (%)	15 (range 1–50)	75 (range 10–75)	50 (range 10–75)
Effect	Better identification of high-risk patients, leading to effective risk reduction strategies. Decrease in sudden cardiac death. May increase invasive procedures such as catheterization and revascularization. Minimal effect on overall cardiac deaths		
Cost	$500 (range $300– $1000)		
From among the candidate imaging tests, the panel unanimously considered MR to be the most likely to achieve widespread application.			

Table 3.1—Continued

MR Angiography as a replacement for coronary catheterization

Eligible population	Clinical disease: potentially all patients with a diagnosis of CAD or CHF
Likelihood of occurrence by 10 years (%)	50 (range 25–70)
Likelihood of occurrence by 20 years (%)	100
Effect	Replacement for conventional coronary angiography, likely to increase in the number of persons undergoing the procedure.
Cost	$1000 (range $500–1500)

Intraventricular cardioverter defibrillators

Eligible population	Subclinical disease: 50% of people with HF, 20% of people post AMI, 20% of people with cardiomyopathy	Clinical disease: patients with (VF/VT)
Likelihood of occurrence by 10 years (%)	30	Already standard of care
Likelihood of occurrence by 20 years (%)	30–40	
Effect	Life expectancy for people with CHF gets shifted by 6–10 months, 20% now die of some other cause.	
	Hospitalizations at the same rate only over a longer period of time due to longer life expectancy.	
	10% (range 5–25%) of patients will have prolonged Activities of Daily Living (ADL) limitations by preventing death in advanced HF or class IV[b] angina.	
Cost	$35,000–40,000 per case	

Left ventricular assist devices (LVAD)

Eligible population	Clinical disease: those patients with a diagnosis of HF, of whom 2–5% will be class IV and the most likely to benefit from early use of a permanent device, possibly increasing to 10% if the studies show class III HF patients also benefit.
Likelihood of occurrence by 10 years (%)	10 (range 5–40)
Likelihood of occurrence by 20 years (%)	50 (range 15–80)
Effect	General level increase in ADL for persons with ADL limitations
	50% decrease in heart failure-related hospitalizations
	20% (range 10–30%) of patients will have improved 1 year mortality
Cost	$120,000 per case (device alone = $70,000)

Table 3.1—Continued

Xenotransplants

Eligible population	Clinical disease: Initially this would be the people currently getting heart transplants plus those ineligible on the basis of limited donor supply. If this technology were perfected, however, the use of such transplants could conceivably be done for indications as diverse as dysrhythmias refractory to conventional drug therapy (as a replacement for implantable cardioverter defibrillator, above) or moderate to severe coronary artery disease (as a replacement for revascularization)
Likelihood of occurrence by 10 years (%)	1–3
Likelihood of occurrence by 20 years (%)	Same
Effect	Possibly similar to the benefit from human heart transplants, but several experts thought the effect would be lower as the population affected is likely to be different.
Cost	Potentially very high. $50,000–100,000

Therapeutic angiogenesis

Eligible population	Clinical disease: As an augmentation for revascularization in potentially 100% of people getting conventional revascularization (identified from ICD-9) and all patients with a diagnosis of peripheral vascular disease.	Clinical disease: As a replacement for revascularization in 5% of those currently considered for revascularization (identified by proxy via a CPT for coronary catheterization).
Likelihood of occurrence by 10 years (%)	10 (range 0–100) as augmentation;	5 as replacement for revascularization
Likelihood of occurrence by 20 years (%)	no comment	10 as replacement for revascularization
Effect	Little effect on mortality	
	Decreased number of revascularization procedures by 20_30% (range 0–80%)	
	Increased ADL by 10–20% (range 10–50%) due to less angina	
	Decreased hospitalization by 20% (range 0–50%)	
Cost	$3000-5000 per case	
NOTE: The likelihood decreases over time because the panel thought this technology would likely be replaced in 20 years by other technologies.		

Table 3.1—Continued

Transmyocardial Revascularization

Eligible population	Clinical disease: 5% of people who get a cardiac catheterization (these represent those not eligible for revascularization)	Clinical disease: up to 30% who currently undergo revascularization
Likelihood of occurrence by 10 years (%)	50 (range 10–100)	10 (range 10–100)
Likelihood of occurrence by 20 years (%)	0–5 for both (it will be replaced by newer technology)	
Effect	Little effect on mortality	
	Decreased number of revascularization procedures by 20–30% (range 0–80%)	
	Increased ADL by 10–20% (range 10–50%) due to less angina	
	Decreased hospitalization by 20% (range 0–50%)	
	Slightly increased revascularization procedures	
Cost	Can get directly from current CMS reimbursement schedule.	

Control of atrial fibrillation
Pacemaker/defibrillators:

Eligible population	Clinical disease: all patients with ICD-9 of chronic AF or paroxysmal AF
Likelihood of occurrence by 10 years (%)	50
Likelihood of occurrence by 20 years (%)	50 (range 5–75). Some panelists expressed the opinion that it will likely be superceded by ablation technologies in 20 years.
Effect	Decreased stroke by 50% (range 5–80%) of the attributable fraction due to AF
	50% (range 0–100%) decrease use of coumadin.
	50% (range 10–70%) decrease in hospitalizations of those due to recurrent AF
Cost	$20,000 to $40,000

Table 3.1—Continued

Catheter-based ablation techniques

Eligible population	Clinical disease: all patients with ICD-9 of paroxysmal AF
Likelihood of occurrence by 10 years (%)	20 (range 10–40)
Likelihood of occurrence by 20 years (%)	20 (range 10–40)
Effect	Decreased stroke by 50% (range 2%–70%) of the attributable fraction due to AF
	50% (range 0%–100%) decrease use of coumadin.
	20% (range 5%–50%) decrease in hospitalizations
	10% (range 5%–10%) increased need for pacemakers
Cost	$10,000 to $17,000

NOTES: ADL, Activities of Daily Living; AF, Atrial Fibrillation; AMI, Acute Myocardial Infarction; AWP, Average Wholesale Price; CAD, Coronary Artery Disease; CHD, Coronary Heart Disease; CHF, Congestive Heart Failure; CMS, Centers for Medicaid & Medicare Services; CVD, Cardiovascular Disease; CPT, Current Procedural Terminology; HF, Heart Failure, ICD-9, International Classification of Diseases, 9th Edition; MR, Magnetic Resonance; VF/VT, Ventricular fibrillation/ventricular tachycardia.

[a] What follows does not consider MR as a replacement for conventional coronary catheterization in order to determine anatomy.

[b] *Class I:* No discomfort (i.e. dyspnoea, palpitation or anginal pain) on ordinary activity; *Class II:* Discomfort on ordinary activity; *Class III:* Discomfort on less than ordinary activity; *Class IV:* Dyspnoea at rest.

BIOLOGY OF AGING AND CANCER

Based on the results of the nominal group process, the original list of eight potential breakthroughs was modified and refined to the following seven topics, which were then discussed in more detail.

- **Telomerase Inhibitors**

  All nuclear DNA contains short sections, known as telomeres, which are attached to the ends. With each cell division and DNA replication, one telomere is lost. At a certain critical low level of telomeres, no more DNA replication, hence, no further cell division, can occur, and in some cases the cell begins to senesce and die. It is widely thought that this process is an evolutionary defense mechanism against cancer. Most cancer cells express telomerase, an enzyme that inhibits the shortening of the telomere string, thus enabling an infinite number of cell divisions. Telomerase inhibitors are small molecules that act to stop the enzyme telomerase, rendering cancer cells again subject to a finite number of divisions and preventing cancer from spreading.

- **Cancer Vaccines**

  Attempts to stimulate the body's immune system to fight cancer cells (analogous to vaccines to prevent viral diseases) have been ongoing for more than 20 years. This topic considers what might occur if these efforts prove successful.

- **Selective Estrogen Receptor Modulators**

  Estrogen is now known to play a role in many physiologic processes of both men and women, including the development of various cancers, osteoporosis, heart disease, cognition, and blood clotting. The difficulty is developing estrogen-like drugs that produce the beneficial effects (prevention of osteoporosis, heart disease, and cognitive decline) without the deleterious effects (increasing the risk of cancer and blood clotting).

- **Antiangiogenesis**

  This topic involves the use of human anti-growth factors that inhibit the development of new blood vessels, a prerequisite for the growth of cancer masses beyond about 1 centimeter in diameter.

- **Diabetes**

  Type 2 (adult-onset) diabetes mellitus occurs in up to 10 percent of elderly individuals and is a risk factor for heart disease, renal failure, and blindness. The primary pathophysiologic derangement in type 2 diabetes is the loss of sensitivity of peripheral tissues to insulin. This breakthrough considers the development of a drug that would increase the sensitivity of peripheral tissue to insulin and thereby prevent the development of the disease.

- **Compound that Extends the Life Span**

  It has been known for years that restricting the caloric intake of mice and rats by 30 percent results in an approximate 25 percent extension in life expectancy. The mechanism underlying this effect is unknown. This topic considers a mythical compound that could be taken by humans that reproduces the effect of caloric restriction in rodents.

- **Compound that Improves Cognition**

  Cognitive ability is defined as memory capacity and speed of information processing. The subject of this topic is a mythical compound that would be taken by everyone and that would slow down the age-related decline in cognitive ability, analogous to existing unproven claims for some nutritional supplements. The reason for inclusion of this topic in the category of biology of aging and cancer rather than in the neurology category was that, according to the process we used, the panels selected the topics they wished to consider.

The results of the group process for each potential breakthrough in the biology of aging and cancer are depicted in Table 3.2.

Table 3.2. Summary Results of Biology of Aging and Cancer Medical Technical Expert Panel

Telomerase Inhibitors

Eligible population	Of 50% of the patients with solid tumors present (local disease), 50% of those will be eligible Of 50% of the patients with disseminated disease, 10% of those will be eligible
Likelihood of occurrence by 10 years (%)	50–60
Likelihood of occurrence by 20 years (%)	0 if ineffective; 100 if effective
Effect	Mortality: 50% will be cured; 50% will have a 25% prolongation of life (wide confidence interval 10-50) Morbidity: minimal effect. Possibility of immune compromise downstream. Possibility of skin problems and fertility problems.
Cost	Similar to AZT (AWP = $176.95 for 100 100mg capsules)

Cancer Vaccines

Eligible population	Patients with both solid tumors and leukemia/lymphomas. Of 50% of the people with local disease, 50% will be eligible. Of 50% of the people with systemic disease, all will be eligible.
Likelihood of occurrence by 10 years (%)	0–10
Likelihood of occurrence by 20 years (%)	10–20
Effect	Melanoma /renal cell carcinoma could be cured. All other cancers could have a 25% boost in survival Morbidity: minimal effect
Cost	Possibly 2–3 times more than the hepatitis vaccine (AWP = $195.26 for 3 doses)

Table 3.2—Continued

Selective Estrogen Receptor Modulators

Eligible population	100% of the population (men and women)
Likelihood of occurrence by 10 years (%)	50
Likelihood of occurrence by 20 years (%)	90
Effect	Areas affected: -Breast cancer decrease of approximately 30% -Osteoporosis (increase spinal bone density in osteoporotic women by 2%) -Prostate cancer (reduce incidents by modest amount) -Endometrial cancer (ameliorate any increased risk due to current hormone replacement therapy by substitution) -Lipids/ cardiac events (reduce cholesterol by 5–10%, reduce LDL by 10%) -Cognitive function (relative risk of Alzheimer's disease 0.40–0.80) -Clotting/DVT (increase risk by 2–3 fold) -Decrease damage after stroke
Cost	Similar to Raloxifene (AWP = $59.40 for 30 tabs of 60 mg pills)

Antiangiogenesis

Eligible population	Potentially all solid tumors; even as an adjunct to local disease resection. Could be given in combination with other therapies
Likelihood of occurrence by 10 years (%)	70–100
Likelihood of occurrence by 20 years (%)	70–100 or go to 0 if shown to be ineffective
Effect	Cure for metastatic disease in 10–50%
Cost	Similar to GCSF or EPO (AWP for EPO = $120 for 10,000 units)

Diabetes

Prevention via insulin sensitization drugs

Eligible population	Of the 80,000,000 obese, 10% develop diabetes mellitus. Best "targeting" may be 30% or 24,000,000
Likelihood of occurrence by 10 years (%)	50
Likelihood of occurrence by 20 years (%)	65
Effect	50% prevention in Type 2 over >5 years (10–15 years)
Cost	Current cost of a glitazone. (AWP for Rosiglitazone = $108.25 for 60 2mg tabs)

Table 3.2—Continued

Compound that Extends Life Span [a]

Eligible population	Everyone. Treatment will start at a younger age because it may take >30 years to start having its beneficial effect.
Likelihood of occurrence by 10 years (%)	0–15
Likelihood of occurrence by 20 years (%)	0–50
Effect	10–20 years of extra life of an equivalency between 20–50 years of age
Cost	Like cumulative costs of nutritional supplements, etc., approximately $1/day; maybe more if a synthetic drug.

Compound that Improves Cognition

Eligible population	Everyone
Likelihood of occurrence by 10 years (%)	0–5
Likelihood of occurrence by 20 years (%)	20
Effect	-Decrease in traffic accidents due to reflex ability (See the existing data for accidents in elderly.) -Decrease in pedestrian accidents due to reflex ability (See the existing data for accidents in elderly.) -Increased period of participation in the workforce -Indirect effect on mortality -Possible effect on ADL through Alzheimer's or other illnesses -Less depression
Cost	$1–2/day

NOTES: ADL, Activities of Daily Living; AWP, Average Wholesale Price; DVT, Deep Venous Thrombosis; EPO, Erythropoetin; GCSF, Granulocyte Colony Stimulating Factor; LDL, Low-Density Lipoproteins.

[a] A mythical compound X that reproduces to some extent the effect of caloric restriction in rodents.

NEUROLOGICAL DISEASES

Based on the results of the nominal group process, the original list of four potential breakthroughs was expanded to the following ten subtopics, which were then discussed in more detail. In contrast to the preceding two panels, this group organized their breakthroughs around specific neurological conditions.

- **Alzheimer's disease**
  - Better identification of persons at increased risk
  - Primary prevention utilizing compounds based upon the amyloid hypothesis
  - Primary prevention utilizing existing or new drugs/compounds
  - Treatment of established disease by vaccine, secretase inhibitor, antioxidants, anti-inflammatories, or selective estrogen receptor modulators (SERMs)
  - Treatment of established disease by cognition enhancers.
- **Parkinson's disease**
  - Treatment of Parkinson's disease by neurotransplantation
  - Prevention and treatment of Parkinson's disease by profiling genetic predisposition for susceptibility to environmental toxins.
- **Acute stroke**
  - Treatment of acute stroke using drugs that minimize cell death
  - Treatment of acute stroke using stem cells to restore neurological function.
- **Depression**
  - Better treatment of existing disease by existing or new drugs.

The results of the group process for each potential breakthrough in neurological diseases are depicted in Table 3.3.

Table 3.3. Summary Results of Neurological Breakthroughs
Medical Technical Expert Panel

ALZHEIMER'S DISEASE (AD)

AD Better Identification of Risk

By genetic profiling and/ or metabolic analysis

Eligible Population	Everybody (can start at age 45 for this model)
Likelihood [a] at 10 years (%)	Median 5 (range 2–15)
Likelihood [a] at 20 years (%)	Median 30 (range (10–50)
Effect	No direct effect on mortality or morbidity, but it will identify people at higher risk for guided treatment
Cost	$250–$3000 when it is steady state

AD Primary Prevention

By things related to the amyloid hypothesis such as vaccine or secretase inhibitor
Current rate of progress from diagnosis to death is about 10 years.
Mild slowing of progression is defined as 20–25%, Moderate is defined as 50%.

Eligible Population	High-risk people identified through profiling, early disease or mild cognitive impairment
Likelihood [a] at 10 years (%)	Median 20 (range 5–20)
Likelihood [a] at 20 years (%)	Median 40 (range 10–50)
Effect	Delay of onset by median 5 years (range 3–10 years) Slow progression by a mild to moderate amount
Cost	Secretase: Similar to statins (AWP varies from $36.60 to $61.86 for one month's supply), maybe as high as protease inhibitors (AWP varies from $463.50 to 667.80 for one month's supply) Vaccine: $1000/shot, will need multiple shots, 2–3 initially and then at least one every 15 years

Table 3.3—Continued

AD Primary Prevention
By existing or new drugs/ compounds like antioxidants, anti-inflammatory agents, or SERMs
Current rate of progress from diagnosis to death is about 10 years.
Mild slowing of progression is defined as 20–25%, Moderate is defined as 50%.

Eligible Population	Everybody or close to everybody
Likelihood [a] at 10 years (%)	Median 25 (range 10–60)
Likelihood [a] at 20 years (%)	Median 40 (range 20–60)
Effect	Delay of onset by 2–5 years Minor effect on progression
Cost	As existing prices (AWP) for cox-2 inhibitor Rofecoxib $72 for one month's treatment; AWP for Raloxifene (SERM) is $59.46 for one month's supply

AD Treatment of Established Disease
By vaccines, secretase inhibitors, antioxidants, SERMs, etc.
Current rate of progress from diagnosis to death is about 10 years.
Mild slowing of progression is defined as 20–25%, Moderate is defined as 50%.

Eligible Population	Established AD (realize that "AD" diagnosis may in the future encompass lesser degrees of symptoms.)
Likelihood [a] at 10 years (%)	Median 15 (range 10–30)
Likelihood [a] at 20 years (%)	Median 30 (range 20–50)
Effect	Decrease in rate of progression that is mild to moderate
Cost	Secretase: Similar to statins (AWP varies from $36.60 to $61.86 for one month's supply), maybe as high as protease inhibitors (AWP varies from $463.50 to $667.80 for one month's supply) Vaccine: $1000/shot, will need multiple shots, 2–3 initially and then at least one every 15 years Antioxidants, SERMs, others at existing prices (AWP for Raloxifene [SERM] is $59.46 for one month's supply)

Table 3.3—Continued

AD Treatment of Established Disease
By cognition enhancers
Current rate of progress from diagnosis to death is about 10 years.
Mild slowing of progression is defined as 20–25%, Moderate is defined as 50%.

Eligible Population	Established and symptomatic mild cognitive impairment
Likelihood [a] at 10 years (%)	Median 25 (range 10–50)
Likelihood [a] at 20 years (%)	Median 40 (range 10–70)
Effect	Shifts back in time by 6 months to 2 years but does not modify the disease
Cost	Pill you could take every day. Standard pricing for patent-protected drug (AWP for cholinesterase inhibitors varies from $137 to $170 for one month's supply).

PARKINSON'S DISEASE (PD)

Treatment of PD
By neurotransplantation and/or stimulation of endogenous precursors

Eligible Population	Established diagnosis of PD
Likelihood [a] at 10 years (%)	Median 10 (range 10–15)
Likelihood [a] at 20 years (%)	Median 25 (range 15–50)
Effect	Shifts back in time by 2 to 5 years but does not modify disease
Cost	$10,000–$30,000 per case

Prevention and Treatment of PD
If PD is caused by combination of environmental toxins and genetic predisposition. May also involve profiling of patients for susceptibility.

Eligible Population	Might be everybody in the absence of profiling, or with profiling only those at high risk
Likelihood [a] at 10 years (%)	Median 5 (range 1–25)
Likelihood [a] at 20 years (%)	Median 10 (range 1–25)
Effect	Eliminate disease in median 15% (range 5–50%) of cases Delay onset in 15–20% of cases
Cost	Lifestyle changes, maybe an antioxidant or new environmental regulation (like cost to repair problems caused by asbestos)

Table 3.3—Continued

ACUTE STROKE

Treatment of Acute Stroke

By drugs given to minimize cell death (neuroprotective drugs)

Eligible Population	In theory, everyone with an acute stroke
Likelihood [a] at 10 years (%)	Median 40 (range 25–50)
Likelihood [a] at 20 years (%)	Median 60 (range 50–75)
Effect	Decrease in disability due to stroke (hospital stay unaffected) of median 30% (range 25–50%) Decrease in rehabilitation period of median 25% (range 10–33%)
Cost	$3,000–$4,000

Treatment of Acute Stroke

Use of neurotransplantation of stem cells to restore neurological function

Eligible Population	All with acute stroke (in theory) or Subset of people who did not respond to other therapies (the 20–30% who don't die and don't recover well)
Likelihood [a] at 10 years (%)	Median 2 (range 2–5)
Likelihood [a] at 20 years (%)	Median 20 (range 5–20)
Effect	Decrease in disability due to stroke of 25% (25–50%)
Cost	$10,000–$30,000

DEPRESSION

Better Treatment of Existing Disease

Substance P, CRF, other new drugs, combined possibly with profiling to determine optimal therapy.

Eligible Population	Depression and dysthymia diagnosis
Likelihood [a] at 10 years (%)	Median 30 (range 25–50)
Likelihood [a] at 20 years (%)	Median 70 (range 50–75)
Effect	70% improvement in symptoms (e.g., 35% improvement over placebo) NOTE: Existing drugs produce a 50% improvement vs. 32% improvement in placebo group; from Evidence-based Practice Centers (EPC) Evidence Report on depression
Cost	Patent-protected drugs equivalent to current drugs (AWP for SSRIs varies from $59.70 to $71.10 for one month's supply). Profiling as before $250–$3,000

NOTES: AWP, Average Wholesale Price; CRF, Corticotropin Releasing Factor; EPC, Evidence-Based Practice Center; SERMs, Selective Estrogen Receptor Modulators; SSRIs, Selective Serotonin Reuptake Inhibitors.

[a] "Likelihood" is defined as that fraction of the eligible population who will receive it.

HEALTH CARE SERVICES

Unlike the topics considered by the preceding three panels, the fourth topic was more generic in focus. The geriatric advisory panel recommended that this panel consider improvements in the organization and delivery of health services that would increase the use of interventions already known to be effective. In addition, panelists were asked to consider diseases such as diabetes that did not fall precisely into other specialty domains. Therefore, the panel did not receive a literature review in advance. For this topic, the panel discussed the following:

- **Increasing the use of known effective interventions**

  This category includes increased compliance with evidence-based effective medicine, examples of which would include the use of computerized feedback, guidelines embedded in computerized medical record-keeping software, better information technologies, the expanded use of continuous quality improvement techniques, expanding the health care quality improvement project, increased consumer demand for more effective care, the public release of performance data, changes in regulation, and changes in Medicare benefits, all of which might be expected to increase compliance.

- **Care coordination**

  This category includes any mechanism by which community services could be better coordinated with medical care.

- **Improved detection of under-diagnosed conditions**

  In particular, the panel was concerned here with better detection, and therefore treatment, of the conditions most common in elders, including osteoporosis, depression, diabetes, falls, anxiety disorders, vision impairment, dementia, hearing impairments, and urinary incontinence.

- **Better medication management**

  Examples of existing technology that can perform this function include the use of hand-held devices such as palm pilots that contain information on drug-drug and drug-disease interactions, computerized order entry, pharmacy programs to identify ill-advised drugs, and reminder systems or other methods to improve adherence for patients.

- **Environmental improvements**

  The principal example discussed by the panel was the increasing use of information technology in the home, such that streaming video robotics could be used to check blood pressures and advise patients on diet, compliance, and other aspects of chronic disease management.

- **What existing secular trends in lifestyle changes are likely to show over the next 10 and 20 years**

  This category focused on the lifestyle behaviors that are most associated with adverse outcomes, including physical activity, obesity, diet composition, cigarette smoking, and the use of alcohol.

  The results of the group process for each topic in health services are depicted in Table 3.4.

Table 3.4. Summary Results of Health Services Technical Expert Panel

Increased compliance with evidence-based effective medicine

Eligible Population	Everybody
Likelihood at 10 years (%)	55 (range 50–60)
Likelihood at 20 years (%)	80 (range 60–80)
Effect	Very high, approximately equivalent to improving the control of hypertension by 25%–50%
Cost	Varies

Eligible Population	Chronic Disease Group: coronary artery disease, congestive heart failure, atrial fibrillation, osteoporosis, osteoarthritis, diabetes mellitus, degenerative joint disease, hypertension, depression, increased cholesterol, chronic obstructive pulmonary disease, asthma, post-stroke, Alzheimer's disease, Parkinson's disease
Likelihood at 10 years (%)	70 (range 60–80)
Likelihood at 20 years (%)	90 (range 80–90)
Effect	Very high
Cost	Varies

Table 3.4—Continued

Care Coordination
defined as coordinating community services with medical care

Eligible Population	"Vulnerable" —high utilizers, using the P_{RA} (Boult et al, 1993) or similar metric
Likelihood at 10 years (%)	80 (range 60–85)
Likelihood at 20 years (%)	90 (range 80–90)
Effect	Modest. Approximately equivalent to improving the control of hypertension by 5–10%. Change in function will be slight if any. Main benefit will be on utilization.
Cost	$500–$1500 per year per person

Improved detection of under-diagnosed conditions
Such as: depression, osteoporosis, diabetes, falls, anxiety disorder, vision, dementia, hearing, urinary incontinence

Eligible Population	Undiagnosed population. Current estimates of under-diagnoses of depression, diabetes, or dementia are that perhaps only half of cases are diagnosed.		
	Depression	Diabetes	Dementia
Likelihood at 10 years (%)	30 (range 10–40)	50 (range 50–75)	30 (range 20–50)
Likelihood at 20 years (%)	Same	Same	Same
Effect	Improvement in outcomes for undiagnosed approximately the same as existing evidence for diagnosed patients.		
Cost	$5/ person tested	$5/ person tested	$5/ person tested

Medication Management
Examples include:
- hand-held drug-drug and drug-disease interaction
- pharmacy programs to identify ill-advised drugs
- Computerized order entry
- Reminder systems or other methods to improve adherence

Eligible Population	Everyone
Likelihood at 10 years (%)	100 (range 90–100)
Likelihood at 20 years (%)	100
Effect	Moderate sized effect on: – reduced hospitalization/ shortened stay – decreased mortality – increased function
Cost	Varies depending on method

Table 3.4—Continued

Environmental Improvements
Examples include home-based platforms, streaming video robotics that check blood pressure (BP), advise you on diet and compliance, etc.

Eligible Population	Chronic disease population such as diabetes mellitus, congestive heart failure, asthma
Likelihood at 10 years (%)	50 (range 20–80)
Likelihood at 20 years (%)	85 (range 40–95)
Effect	For people with chronic disease, similar to other chronic disease management programs aimed at decreasing utilization
Cost	About the same as a personal computer (if mass production is possible)

Current trends in lifestyle changes [a]

	Physical activity	Obesity	Diet composition	Smoking	Alcohol
Current Trend	no trend	greatly increasing	improving	decreasing	possibly worsening in the elderly
Eligible population	everybody	everybody	everybody	cigarette smokers	everybody
Change in trend after 10 yr	15% (range 5%–15%)	0% (range -5%–7.5%)]	-5%	stable	0% (range -10%-0%)
Change in trend after 20 yr	15% (range 5%–20%)	0%	-5% (range -10%-0%)	stable	same
Assumptions about the current lifestyle	assume 15% baseline for exercise in elderly	assume 35% obese, increasing trend	assume 40% cal from fat	metric for smoking existing econometric model	40% over age 65 at risk for misuse of alcohol

Notes: P_{RA},Probability of Repeated Admission (screen).
[a] A positive number indicates an expected increase, a negative number indicates an expected decrease, and "no trend" indicates no apparent pattern of change with time. We are unable to estimate the costs for lifestyle changes because it is hard to quantify either the value or the costs associated with lifestyle changes.

CHAPTER 4:
THE FUTURE ELDERLY MODEL

At the core of our model development is a demographic-economic model the primary function of which is to project future health care expenditures and health status. The second function of this model is to serve as the simulation vehicle for evaluating what-if scenarios about the future health care environment. The model diverges from traditional approaches in that it includes a multidimensional characterization of health status. In addition, conventional actuarial approaches employ cell-based models in which each cell represents a subpopulation of interest. While it is theoretically possible to extend cell-based models to support health care projections, practical shortcomings make it difficult to simulate changes of the sort identified by our expert panels. The desirability of a rich characterization of health status, by sex and age group, implies that the number of cells would need to be very large. Cell sizes would be correspondingly small, and the very large Markovian transition probability matrix difficult to estimate. Microsimulation models offer a conceptually and analytically superior alternative.

To guide the process of model development, RAND enlisted the help of a panel of social scientists from around the country. For more details about the processes they used, see Appendix B.

THE MECHANICS OF THE FUTURE ELDERLY MODEL

Microsimulation models begin with as large a sample of individuals as possible. The sample must contain information on all health status measures that are strong predictors of health expenditures. For expositional purposes, suppose health measures A, B, and C are relevant. In our preliminary specification, these measures reflect activities of daily living (ADLs), clinical diagnoses (cancer, diabetes) or perhaps states such as institutionalized in a nursing home. The states are not mutually exclusive, e.g., an individual may both suffer from diabetes and be institutionalized. In addition, the measures may or may not be "absorbing," that is, an individual may recover from a subset of health statuses. We denote with H the healthy state in which the person is free from A, B, and C, and with D the deceased state. Individuals may then be H; A; B; C; A+B; A+C; B+C; A+B+C; or D.

At the time the sample was drawn, we knew the individuals' health statuses. The goal was to map out the individuals' remaining life paths and identify at what point(s) in time they will transition into other health statuses and when they are likely to become deceased. This process requires that we estimate transition models into all possible health states. In our example, we need at least four models: transition into A; transition into B; transition into C; transition into D (deceased), plus additional potential recovery models. We don't need to distinguish, say, transitions H→B from A→A+B; the fact that an individual suffers from A may be treated like any other covariate, so that the models are conditional on existing health status.

The first step is to estimate individual health transition models. Several types of models may be chosen, depending on the richness of available (longitudinal) data. For example, a simple logit or probit transition model may be estimated if information is available on health status at

two points in time. With more than two health status observations per individual, such simple models may account for health history; with yet more detailed information, continuous-time hazard models may be estimated. Transition models may be estimated using any data source that contains health measures that are identical to those distinguished in the microsimulation sample. Preferably, transition models should be estimated directly off the microsimulation sample, so that the definition of health outcomes is exactly right.

The second step is to project future health transitions. Regardless of the estimated model type, we can compute interval (discrete) transition probabilities conditional on a rich set of demographics, current health status, and (if available) health status history. These transition probabilities are used to forecast health transitions. If the probabilities account for current information only, a first-order Markovian process is generated; if they account for lagged covariates, such as accumulated health histories, higher-order Markovian processes result. Note that the probabilities depend on potentially many individual-specific characteristics and initial states, unlike the generic transition probabilities in cell-based models, which apply to cells consisting of a fairly heterogeneous subpopulation.

By illustration, consider an individual who at baseline suffers from health condition A. The model computes the following four transition probabilities:

1. probability of recovering (transition into state H) in the next year (say, $p_h = .002$);

2. probability of attracting health condition B (transition A→A+B) in the next year (say, $p_h = .06$);

3. probability of attracting health condition C (transition A→A+C) in the next year (say, $p_h = .05$);

4. probability of dying (transition A→D) in the next year (say, $p_h = .08$).

We draw a random number between zero and one from a uniform distribution, to simulate a health shock. If the transition probability exceeds the corresponding random draw, we project that the transition took place. It may well be that all four random draws are larger than the transition probabilities. In that case, the person remains in state A throughout the year. It may also be that multiple transitions are projected to take place. In the example, transitions into both B and C may be possible, so that the person ends up with multiple health conditions, A+B+C. The transition into death logically dominates all others. If multiple transitions are conceptually implausible or impossible, the transition interval may be shortened (from a year to perhaps just a week or a day), so that multiple transitions are ruled out.

Continuing the example, suppose the model projects that the individual will remain in state A throughout the first year. Transition probabilities for the next year change, because the individual is one year older, and perhaps because there are time trends in the transition models. We then draw new random numbers. If the individual remains in state A for four additional periods (until the sixth period), he or she is projected to develop illness B, so his or her new state is A+B. Then, the set of potential next transitions changes. Further, the transition probabilities have changed, not just because of age and time, but also because of a change in health condition. For example, the individual's health has now deteriorated severely so that his or her mortality

risk is much higher than before. We compute new transition probabilities and compare them with randomly drawn numbers. The result is a simulated life path in which the individual accumulates multiple disease conditions and then dies.

CHOICE OF THE HOST DATA SET

The microsimulation sample needs to be a large database with information on many personal characteristics: sex, date of birth, health conditions, income, supplemental health insurance status, and as many other covariates as possible. These requirements suggest the need for large-scale survey data: This database is the host survey.

After consultation with the social science expert panel, we chose to use the Medicare Current Beneficiary Survey (MCBS). The MCBS is a nationally representative data set designed to ascertain utilization and expenditures for the Medicare population, especially those expenditures borne by the beneficiary or supplemental insurance. The sample frame consists of aged and disabled beneficiaries enrolled in Medicare Part A and/or Part B, although we use only the aged. The MCBS attempts to interview each person twelve times over three years, regardless of whether he or she resides in the community or a facility, or transitions between community and facility settings. The disabled (under 65 years of age) and the oldest elderly (85 years of age or over) are oversampled. The first round of interviewing was conducted in 1991. Originally, the survey was a longitudinal one with periodic supplements and indefinite periods of participation. In 1996, the MCBS switched to a rotating panel design with limited periods of participation. Each autumn a new panel is introduced, with a target sample size of 12,000 respondents, and each summer a panel is retired. The MCBS contains detailed self-reported information, including the prevalence of various conditions; measures of physical limitation in performing ADLs and instrumental ADLs (IADLs); and height and weight. In addition, the MCBS contains detailed self-reported data on health service use, as well as Medicare service use records. Institutionalized respondents are interviewed by proxy. Table 4.1 shows the MCBS sample size in each year from 1992 to 1998.

Table 4.1. MCBS Sample Size, 1992 to 1998

Year	N	Percent
1992	10,584	14.6
1993	10,188	14.1
1994	10,557	14.6
1995	9,974	13.8
1996	9,866	13.6
1997	10,426	14.4
1998	10,881	15.0
Total	72,476	100.0

We selected all individuals age 65 and older in the MCBS 1998 data set, and dropped individuals with any missing health status information (most dropped respondents had missing information on neurological disorders). This process left 10,881 individuals. Original MCBS cross-sectional weights indicate the number of persons in the population that every sample

member represents. The weights range from 1106 to 12,131 due to stratified survey sampling and non-response rates. We re-scaled the weights such that they added up to the 1998 population of individuals aged 65 and older.[1] A simulation with this host data set of 10,881 individuals would generate unbiased projections. However, the sample size for rare subpopulations (as measured by their multidimensional health status) is limited. We therefore replicate observations in the sample, which allows for multiple health status paths per sample member and yields more precise (smoother) estimates of future health status distributions. We replicate in accordance with individuals' relative weight in the sample; the minimum number of replications is two, the maximum 55. The average replication is ten times, so that the resulting host data set consists of 108,810 individuals. Their weights are now more uniform and range from 276 to 355.

DEFINING HEALTH STATES

Our choice of health status measures must meet several competing goals. First, they should predict costs. Second, they should capture clinically relevant diseases that will be useful for predicting the effects of our breakthrough technologies. Third, they should be readily available in the MCBS and other data sets that will provide estimates for the microsimulation—e.g., the National Health Interview Survey.

We define health states based on self-reported health conditions and disability. The MCBS asks about a multiplicity of health conditions. For the preliminary model, we chose to focus our analysis on diseases being investigated by our medical panels. Because of the way these diseases were chosen, these conditions are the ones that are most prevalent in the elderly population and also the most expensive to treat. The conditions we use are shown in Table 4.2 along with their prevalence in the MCBS. For comparability with other studies, these rates exclude individuals residing in a facility at any point during the year.

[1] This population consists of 34,385,239 individuals. Population estimates for 1998 through 2030 are taken from the Census Bureau.

Table 4.2. Prevalence of Select Conditions, MCBS Non-Institutionalized Population

	MCBS Prevalence by Age (%)		
Condition	**65+**	**65–69**	**70+**
Cancer	17.7	14.3	19.0
Breast[a]	6.5	6.8	6.4
Prostate[b]	6.6	4.3	7.5
Uterus[a]	2.9	2.4	3.0
Colon	2.5	1.6	2.9
Bladder	0.9	0.3	1.1
Lung	1.0	0.9	1.1
Kidney	0.3	0.3	0.3
Throat	0.5	0.2	0.7
Head	0.2	0.1	0.3
Brain	0.1	0.1	0.1
Other	3.1	2.7	3.3
Heart Disease	38.2	29.5	41.4
Angina pectoris/CHD	14.4	11.3	15.5
Myocardial infarction	14.7	12.4	15.6
Other	27.6	20.4	30.4
Alzheimer's	2.4	0.7	3.0
Stroke	10.4	7.4	11.5
Diabetes	16.0	15.2	16.3
Hypertension	55.8	49.5	58.1
Lung	14.2	13.7	14.4
Arthritis	57.3	48.5	60.6
BMI[c]	26.0[c]	27.1[c]	25.5[c]
Ever smoke	60.3	64.4	58.8
Disability			
ADL≥1	25.8	16.1	29.4
ADL≥3	8.4	3.7	10.2

NOTE: Results from 1998 MCBS survey sample. Responses are weighted using MCBS 1998 cross-sectional weights.

[a] Universe includes women only.

[b] Universe includes men only.

[c] Not in percentages.

As a consistency check, we compared several of these rates from MCBS 1995 with data from the 1994 and 1995 National Health Interview Surveys. The NHIS serves as the data source for the under-65 population who will age into Medicare in the microsimulation. The result of this comparison is shown in Table 4.3.

Table 4.3. Comparison of Condition Prevalence between the MCBS and NHIS

	MCBS Prevalence by Age (%)			NHIS Prevalence by Age (%)		
Condition	**65+**	**65–69**	**70+**	**65+**	**65–69**	**70+**
Cancer	19.3	15.9	20.7			
Breast [a]	6.6	6.2	6.7	2.6	1.5	3.1
Prostate [b]	5.8	4.4	6.4	4.5	2.6	5.5
Uterus [a]	3.1	2.9	3.1	0.2	0.2	0.2
Colon	2.3	1.2	2.8	0.6	0.4	0.7
Lung	0.8	0.8	0.8	0.4	0.1	0.5
Heart Disease	38.3	30.2	41.7	27.5	21.5	30.2
Hypertension	54.4	47.9	57.1	36.4	30.8	38.9
Diabetes	17.2	16.0	17.6	10.1	8.7	10.8
Disability						
ADL≥1	27.2	17.1	39.4	9.6	4.5	11.9
ADL≥3	9.5	5.0	11.5	4.1	2.0	5.1

NOTES: NHIS prevalence rates are from 1994, except for disability, which comes from the 1995 Disability Phase I supplement. Tabulations are based on the recodes provided by NHIS (Diagnostic Recode C). The NHIS asks about stomach, intestine, colon, and rectal cancer in one question, the response to which is reported as "colon cancer." MCBS data are from 1995.

[a] Universe includes women only.

[b] Universe includes men only.

Clearly, the two sets of prevalence estimates show some large differences. Some of the difference can be explained by question wording. The MCBS asks about all conditions in the form "Has a doctor ever told you [that] you had [condition]?" However, the NHIS varies its wording depending on the condition.[2] For diabetes and the cancers listed above, the questions are of the form "During the past 12 months, did anyone in the family have [condition]?" For cardiovascular disease and hypertension, the NHIS asks, "Has anyone in the family ever had...?" except for tachycardia and heart murmurs, which were surveyed in the form "During the past 12 months, did anyone in the family have...?"

This wording difference means that the rates of cancer reported in the NHIS should be much lower than those in the MCBS, since the NHIS asks only about the previous year. For example, if a woman had an early stage, non-metastatic tumor removed from her breast ten years ago, she would not report this cancer in the NHIS, but she would report it in the MCBS. However, the NHIS has much lower rates of cardiovascular disease,[3] hypertension, and diabetes, which cannot be explained by differences in question wording.

[2]The NHIS does not ask each respondent all conditions. Instead, the family is randomly assigned to one of six condition lists: skin and musculoskeletal conditions; impairments; selected digestive conditions; selected conditions of the genitourinary, nervous, endocrine, metabolic, and blood forming systems; selected circulatory conditions; or selected respiratory conditions. Since the list of cancers crosses condition lists, we cannot calculate an overall prevalence rate for any cancer.

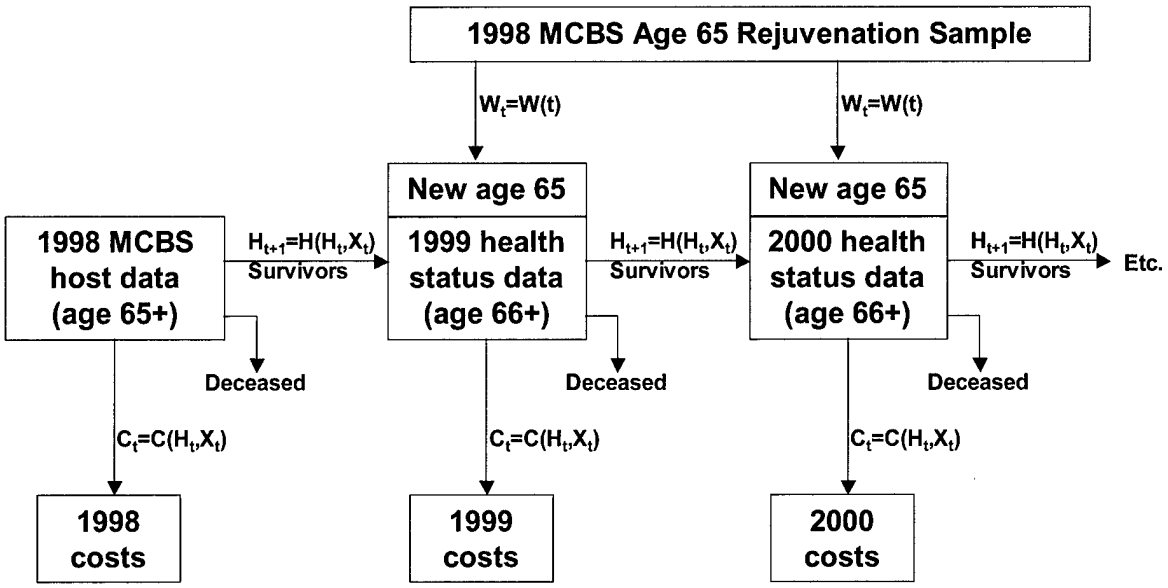
[3]Heart disease includes the following recodes from the NHIS: rheumatic fever with or without heart disease (501); ischemic heart disease (502); heart rhythm disorders, including tachycardia or rapid heart (503), heart murmurs (504), other and unspecified heart rhythm disorders (505); congenital heart disease (506); other selected diseases of the heart (excludes hypertension) (507); and hardening of the arteries (510).

Disability in the MCBS is defined as having any difficulty with performing or inability to perform bathing *or showering*, dressing, eating, getting in and out of bed or chairs, *walking*, and using the toilet. In the NHIS supplement, disability is defined as having any difficulty with performing or inability to perform bathing, dressing, eating, getting in and out of bed or chairs, *getting around inside the home*, and using the toilet. Because the MCBS asks about showering and walking, which results in higher rates of difficulty than that represented by getting around inside the home, it should identify higher rates of disability. These wording differences explain much—but not all—of the differences in disability rates, since the differences persist even when similarly worded ADLs are compared (data not shown).

FUTURE ELDERLY MODEL OVERVIEW

Figure 4.1 depicts how the cost models, transition models, and rejuvenation models are integrated into our microsimulation model. The model is designed to yield predictions in constant dollars and—at baseline—using 1990s technology. We start with MCBS data for 1998 as the host cohort. The characteristics of these individuals are used to predict per capita 1998 medical expenditures based on their sociodemographic characteristics, health status, and functional status. The weights of the host data are adjusted such that they add up to the 1998 population of individuals age 65 and older. The product of per capita expenditures and population size yields aggregate 1998 medical expenditures. These individuals are dropped from the sample. We then project individuals' health and functional status in 1999, including those who die. By then, the sample has aged to 66 years of age and older. We rejuvenate the sample using a rejuvenation sample that consists of 65-year-old MCBS respondents. The weights of newly entering individuals are adjusted, first, in accordance with 1999 prevalence rates of health conditions among 65-year-olds, and second, such that the sum of weights for age 65 in the simulation sample equals the 1999 population of 65-year-old individuals. The resulting sample is representative of the 1999 population age 65 and older. We use the health status and demographic characteristics of this sample to predict per capita 1999 medical expenditures and derive the 1999 aggregate expenditures. We then drop individuals who have become deceased, project the health status of survivors in 2000, rejuvenate the sample, compute 2000 costs, and continue this process for each year through the year 2030.

Figure 4.1. Overview of the FEM



NOTES: 1. C = costs; C_t = costs in a given calendar year; H = health status; H_t = health status during the year of the interview; W = a relative weight; X_t = demographic controls. 2. Costs are predicted in constant (1998) dollars and assume a level of treatment and technology as it existed in the 1990s.

Sample Rejuvenation

As our initial host sample ages, it is no longer representative of the age 65+ population. We therefore rejuvenate the sample annually with a newly entering cohort of 65-year-olds. These individuals consist of 65-year-olds in the 1992–1998 MCBS; each individual enters only once, with his or her characteristics measured as of the first year of the MCBS in which he or she was interviewed.

There are 2,863 65-year-old respondents in the 1992–1998 MCBS. We conducted a separate analysis of the "diversity" of these 2,863 individuals, distinguishing all possible combinations of cancer, heart disease, neurological disorder, hypertension, diabetes, and disability (0 vs. 1+ vs. 3+ ADLs). The number of theoretically possible combinations is 2*2*2*2*2*3 = 96. The 10,881 1998 MCBS respondents of all ages represent 95 health status combinations; the 2,863 65-year-old respondents represent 89 of those combinations. In other words, seven health status combinations are missing among our sample 65-year-olds. Naturally, as individuals age, they may acquire more health conditions and move into new health condition combinations.

Components of the Model

Subsequent chapters describe the three models that form the components of our microsimulation model: health care costs, health status transitions, and characteristics of future newly entering Medicare enrollees. Chapter 5 describes the cost estimation using data from the

MCBS. We consider two outcomes: total Medicare payments and payments from any source. The explanatory covariates include self-reported health status, interactions of health status with disability measures (to capture severity of the condition), residency in a (nursing home) facility, and demographic characteristics. The products of these cost models are functional relationships that predict medical expenditures; we denote these relationships by $C_t = C(H_t,X_t)$.[4] In so doing, we make several assumptions:

1. We assume that future individuals with a given set of health conditions receive the same medical care as individuals in the MCBS. This is tantamount to saying that our baseline case corresponds to 1990s technology.

2. We assume that 1998 unit prices continue throughout our forecast period. This (obviously unrealistic) assumption implies that our results are in 1998 dollars. The applicable price index is the price index for medical services, not the standard consumer price index.

3. Cost regressions are based on non-HMO Medicare enrollees, so our per capita projections apply to the non-HMO population only.

4. We assume that the elderly do not migrate across Census region borders (Northeast, Midwest, West, South, other) as they age. We also assume that elderly who dwell in urban areas continue to do so and that those in rural areas do not move to an urban area.

5. We assume that there are no changes in the age patterns of omitted and potentially time-varying covariates such as marital status and private retiree health insurance coverage. We also convert per capita medical expenditures into population aggregates using elderly population estimates from the Census Bureau.

6. We assume that medical costs of HMO enrollees and the non-HMO elderly are the same.

7. We assume that all elderly are covered by Medicare Parts A and B. This assumption implies a slight overestimate of projected aggregate hospital costs (Part A) and an overestimate of roughly 3 percent of projected aggregate supplemental medical insurance (Part B) costs.

8. We assume the population forecasts do not distinguish race or Hispanic ancestry, so we assume that the fractions of African-Americans and Hispanics remain constant.

Chapter 6 develops models of health transitions. It currently uses only data from the MCBS. We project transitions of self-reported cancer, heart disease, Alzheimer's disease, stroke, diabetes, hypertension, lung disease, arthritis, and disability. Mortality is calibrated to national figures using the National Center for Health Statistics (NCHS) Vital Statistics of the United States (NCHS, 1992-1998), thereby allowing a global time trend in life expectancy. The explanatory covariates include health status and demographic characteristics as measured in the previous year. The product of these transition models are functional relationships that predict health status one year into the future; we denote these relationships by $H_{t+1} = H(H_t,X_t)$. Because these states are measured by questions such as "Did a doctor ever tell you . . . ," we treat them as

[4] For flow variables, such as annual costs, C_t, subscript t denotes a calendar year; for stock variables, such as health status, H_t, it denotes the year of interview (typically administered in the fall).

absorbing. We also project future disability status (number of ADLs), which may improve or deteriorate with age. Finally, we project entry into facilities such as nursing homes: We assume that residence in a facility is an absorbing state.

Chapter 7 describes how we estimate prevalence in future years—i.e., how we forecast the health status of new entrants into Medicare at age 65. Our method uses data from several years of the NHIS and exploits prevalence and incidence rates for individuals as young as 30 years old. It projects joint prevalence rates of cancer, heart disease, neurological disorder, hypertension, diabetes, and disability status among 65-year-olds through the year 2030. In addition, it takes account of co-morbidity patterns of newly entering Medicare enrollees in the MCBS and forces MCBS prevalence correlations to continue in its forecasts. It then rescales projected joint prevalence rates into weight adjustment factors, which are used for annual rejuvenation of the sample with newly entering Medicare enrollees. The products of these trend models are relative weights for each health condition combination for 65-year-olds in 1998 through 2030; we denote these relative weights by $W_t = W(t)$. Before rejuvenating the simulation sample with newly entering 65-year-olds, we adjust their weights in accordance with projected joint prevalence levels. We then apply a second adjustment to the weights of newly entering individuals to ensure that the total population of individuals age 65 and older matches projections from the Census Bureau. Finally, to boost sample size, we replicate newly entering individuals and adjust their weights accordingly.

Our assumption that disability and nursing home residence are absorbing states without allowing for recovery may result in overestimation of disability and nursing home prevalence. FEM does not incorporate supply-side factors such as physician supply and macroeconomic conditions. But the existing FEM can be modified to simulate the effects of changes from inpatient to outpatient services as well as changes in insurance coverage on health conditions and health care costs. The goal of FEM is not to predict future costs, but to evaluate the effects of medical breakthroughs, changes in demographic trends, and changes in health care systems and patient behaviors on health conditions and health care costs of the elderly.

CHAPTER 5:
HEALTH EXPENDITURES

A major determinant of health care expenditures among elderly Americans is the prevalence of chronic disease and disability. Although not all of these conditions lead to persistently high medical costs, the occurrence of a stroke or the presence of cancer, and many other conditions can have a lasting effect on health status, disability, and the demand for medical services.

Efforts to control Medicare expenditures often focus on a minority of beneficiaries who use a disproportionate share of medical services. In 1998, 50.2 percent of older beneficiaries (age 65+) had Medicare reimbursements under $1,000, while 5.7 percent had annual expenses over $25,000. Other studies indicate that 10 percent of beneficiaries account for 75 percent of program outlays each year (Berk and Monheit, 1992). Although cross-sectional Medicare expenditures are highly skewed, recent evidence suggests that beneficiaries with high expenditures tend to have high mortality rates, and those that survive typically have more modest expenses in subsequent years (Garber et al., 1999). This finding suggests that many acute conditions increase expenditures in the near term, but do not have persistent effects on utilization and costs.

The aim of this subtask was to explore the determinants of Medicare expenditures, paying particular attention to the effects of health status, chronic disease, and disability. To maintain consistency with our medical panels, we examined four broad domains of chronic disease: cancer, cardiovascular disease, diabetes, and neurological conditions. These areas were chosen because they are sufficiently prevalent among the elderly, have significant effects on morbidity and mortality, and are likely to have both immediate and long-term effects on health care expenditures.

This chapter summarizes our findings in estimating the determinants of Medicare reimbursements. First, we describe the data and our sample, including the number of enrollees, average Medicare expenditures, and the distribution of medical spending over a seven-year period. We then explore the prevalence and incidence of chronic disease, functional disability, and health status; and their predictive effects on Medical expenditures, both independently and jointly. We then examine the path of medical expenditures over the course of an illness, distinguishing costs associated with incident, maintenance, and terminal phases of care. Finally, we discuss preliminary estimation strategies and analytical approaches to modeling health care costs.

DATA

We use longitudinal data from the Medicare Current Beneficiary Survey Cost and Use files, as described in Chapter 2. Reimbursements in the MCBS are categorized into nine different service groups, such as inpatient care, ambulatory services, outpatient prescription drugs, home health, and institutional care. This level of cost detail allows us to explore how new therapies and technologies affect treatment and outcomes and how the mix of services changes over time and across patient subgroups.

The cost analyses exclude enrollees under age 65 and persons enrolled in HMOs. These exclusions yield an average yearly sample of about 8,600 beneficiaries. All the costs are adjusted by medical Consumer Price Index (CPI) and measured in 1998 dollars.

The annual number of enrollees and average Medicare reimbursements over the seven-year period are reported in Table 5.1. Average Medicare expenditures increased 11.5 percent in real terms between 1992 and 1998, reflecting possibly increased per capita utilization. The number of enrollees in our sample declined over time, primarily due to increased HMO enrollment and greater numbers of younger beneficiaries, who were excluded from the analyses.

Table 5.1. Sample Size and Medicare Reimbursement, by Year

		Medicare Reimbursement	
MCBS Year	N	Mean	Std. Dev.
1992	9,406	$4,441	$11,303
1993	8,966	4,501	11,790
1994	9,212	5,021	13,208
1995	8,469	5,160	13,322
1996	8,073	5,315	13,432
1997	8,200	5,416	13,339
1998	8,325	4,953	11,747
Total	60,651	4,960	12,614

Because we are interested in forecasting future Medicare outlays, the primary cost measures used in the analyses are total Medicare reimbursements and their major components. CMS calculates and projects allowed charges or costs for Medicare-covered services and subtracts the deductibles and coinsurance owed by the beneficiary. Part A reimbursements cover inpatient hospital services, up to 100 days of post-hospital skilled nursing facility (SNF) care, home health services, and hospice care. Part B provides coverage for physician services, outpatient hospital services, durable medical equipment, and other medical and ancillary services. Secondary analyses examine out-of-pocket expenses, Medicaid reimbursements, and medical spending by other third-party payers.

DISABILITY, HEALTH STATUS, AND DISEASE

We first examined how alternative measures of health and disability affect expenditures, both independently and interactively.

Disability. Past efforts to model the effects of medical interventions on utilization and costs typically include various measures of physical health such as functional limitations, disability, or the presence of chronic diseases. Two measures of physical functioning common in survey data are *functional limitations* and *activities*. Functional limitations generally reflect an inability to carry out physical tasks such as bending or lifting without help or aids. Alternatively, activities of daily living are more closely tied to social roles, particularly those deemed necessary to meet an individual's personal needs, e.g., eating, bathing, and dressing. A related concept, instrumental activities of daily living, includes more complex activities, such as managing money and shopping for groceries.

The MCBS asks respondents if they have any difficulty performing each of six daily activities because of health or physical problems. The percent of the sample reporting difficulty with each activity is reported in Table 5.2. Nearly 20 percent of older beneficiaries report difficulty bathing or getting out of bed or a chair; nearly 6 percent have troubling eating; and almost 30 percent report difficulty walking.

Table 5.2. Frequency of Activity Limitations

Condition	Percent of Sample Reporting Difficulty
Bathing	16.9
Dressing	11.9
Eating	5.2
Getting Out of Bed/Chair	16.9
Using the Toilet	9.4
Walking	27.2

SOURCE: 1992–1998 MCBS
NOTE: Observations are weighted by normalized annual cross-sectional weights (weights in each year sum to one).

In aggregate, about 40 percent of older beneficiaries either report one or more ADLs or reside in nursing homes, which are highly correlated with Medicare reimbursements. Beneficiaries age 65 and older who experience difficulties walking, dressing, or getting out of bed have substantially higher medical expenditures than those without limitations (Table 5.3). For example, persons reporting five or more ADLs incur at least $14,629 in annual Medicare expenses compared to less than $2,900 for seniors without limitations (excluding nursing home residents).

Table 5.3. Average Medicare Reimbursement by ADL Counts

ADL Counts [a]	N (Unweighted)	% of Sample	Mean $	Median $
0	36,469	60.1	2,875	451
1	7,242	11.9	5,685	1,071
2	3,751	6.2	6,510	1,361
3	2,098	3.5	9,215	2,514
4	1,665	2.7	10,865	3,271
5	1,634	2.7	14,629	6,649
6	985	1.6	20,675	10,355
Nursing home	6,807	11.2	11,303	3,369

SOURCE: 1992–1998 MCBS
NOTES: 1. Observations are weighted by normalized annual cross-sectional weights (weights in each year sum to one). 2. All costs are in 1998 dollars.
[a] Categories are mutually exclusive.

ADLs are widely used in empirical studies because they are highly predictive of medical care utilization and costs and are easily interpretable. However, ADLs are inconsistently defined across surveys. Disability rates in the MCBS tend to be higher than in other surveys of the same population, particularly the fraction reporting difficulty walking.

Self-reported health status. Another common measure of physical well-being is self-reported health status. The MCBS asks respondents to rate their general health using a five-category Likert scale (excellent, very good, good, fair, poor). The Likert scale is widely used in national surveys and highly predictive of medical expenditures (see Table 5.4). Our data indicate that nearly 70 percent of older beneficiaries report being in good to excellent health, despite the fact that more than 40 percent report one or more ADLs. In addition, the Likert scale of general health status is highly correlated with Medicare expenditures. Older beneficiaries reporting to be in poor general health have nearly three times the costs of those in good health and more than a seven-fold increase in Medicare expenses relative to those in excellent health.

Table 5.4. Medicare Reimbursement by Self-Reported Health Status

Self-Reported General Health	N (Unweighted)	% of Sample	Mean $	Median $
Excellent	8,854	14.6	1,919	233
Very Good	15,012	24.8	2,639	422
Good	18,523	30.5	4,351	794
Fair	12,771	21.1	7,580	1,728
Poor	5,339	8.8	14,640	5,567
Missing	152	0.3	11,149	2,929

SOURCE: 1992–1998 MCBS

NOTES: 1. Observations are weighted by normalized annual cross-sectional weights (weights in each year sum to one). 2. All costs are in 1998 dollars.

The principal limitation of the Likert scale is the difficulty translating advances in medical technologies and treatments to changes in self-reported health states. In other words, how we map input from the Medical TEPs on emerging technologies and treatment breakthroughs into discrete changes in health states is unclear. For this reason, the social science expert panel cautioned against using self-reported health in a forecasting model, preferring more medically based definitions of health status and disease states.

Chronic disease. In addition to including measures of physical functioning and self-reported health states, many studies characterize morbidity by the presence of chronic disease and related symptoms. Table 5.5 shows the average Medicare expenditures by disease conditions. As expected, the average Medicare expenditures per disease condition are about 50 percent higher on average than those per beneficiary, as shown in Table 5.1. Average Medicare expenditures also exhibit large variations within the same condition as well as across conditions. For example, the average Medicare expenditures for brain cancer are about 2.5 times higher than the average Medicare expenditures for uterine cancer. The average Medicare expenditures for stroke are 80 percent higher than the average Medicare expenditures for arthritis.

Table 5.5. Medicare Reimbursement by Self-Reported Conditions

Condition	N (Unweighted)	Mean $
Cancer	11,510	6,775
Breast	2,589	5,823
Prostate	1,786	7,937
Uterine	1,194	5,142
Colon	1,816	7,389
Bladder	548	10,070
Lung	549	12,266
Kidney	253	7,729
Throat	246	10,321
Head	207	6,406
Brain	140	12,764
Other	2,632	7,238
Heart disease	25,124	7,268
CHD	10,272	8,153
Myocardial infarction	9,742	8,853
Other	18,964	7,563
Alzheimer's	4,125	8,363
Stroke	8,335	9,228
Diabetes	10,201	8,079
Hypertension	32,812	5,764
Lung	8,633	7,533
Arthritis	34,205	5,160

SOURCE: 1992–1998 MCBS

NOTES: 1. Observations are weighted by normalized annual cross-sectional weights (weights in each year sum to one). 2. All costs are in 1998 dollars.

Interaction of ADLs and chronic disease. Whereas functional limitations and chronic diseases are correlated with medical care spending, neither measure necessarily explains costs or predicts future health states. For instance, an incident case of cancer may predict higher-than-average expenditures the next year, as the patient receives follow-up therapy. But if the cancer goes into remission or is cured, the patient's expenditures may not be much higher than average in subsequent years (Garber et al., 1999). Similarly, an early diagnosis of prostate or breast cancer may indicate high future expenditures or concern for preventive care and health-conscious behavior that results in low medical costs in the long run. The interaction of chronic disease and functional limitations provides a more accurate assessment of underlying health and medical spending.

Table 5.6 presents average Medicare reimbursements by disease and ADL categories. We categorized ADLs into three groups (0, 1–2, 3+) and defined diseases based on patient self-reports. Medicare expenses rise substantially with increases in physical limitations, particularly among persons reporting three or more ADLs. This pattern occurs consistently across conditions.

Table 5.6. Medicare Costs by Self-Reported Conditions and ADL Counts

Condition	Self-Reported			
	ADL 0	ADL 1-2	ADL 3+	Nursing Home
Cancer	$4,491	$7,284	$14,025	$13,800
Breast	3,808	5,376	11,232	14,788
Prostate	5,866	8,099	17,586	14,102
Uterus	3,144	4,965	11,250	13,004
Colon	5,386	7,791	12,968	12,003
Bladder	7,734	10,637	17,170	23,652
Lung	8,458	10,602	25,446	12,761
Kidney	4,806	10,332	14,526	14,829
Throat	5,326	12,570	31,247	13,043
Head	3,349	9,482	17,527	4,995
Brain	4,397	4,816	24,737	13,001
Other	4,868	7,828	14,618	14,281
Heart	4,670	7,501	14,055	12,355
Angina pectoris/CHD	5,340	8,339	15,621	11,857
Myocardial infarction	5,928	8,783	16,952	14,087
Other	4,769	7,794	14,124	12,288
Alzheimer's	4,111	5,905	11,681	8,765
Stroke	4,776	7,830	15,434	11,942
Diabetes	4,290	8,143	15,992	16,430
Hypertension	3,457	6,256	13,200	12,773
Lung	4,247	8,079	15,033	15,343
Arthritis	3,143	5,726	11,899	11,429

SOURCE: 1992–1998 MCBS

NOTES: 1. Observations are weighted by normalized annual cross-sectional weights (weights in each year sum to one). 2. All costs are in 1998 dollars.

Aggregate measures of disease. The number of disease states is potentially quite large. Our preliminary model takes a conservative approach to this issue by aggregating specific diseases among our clinical domains of primary interest. These domains are then integrated with ADL counts to create disease-disability states, as shown in Table 5.7. ADLs and medical expenditures remain positively correlated; however, the rise in expenditures associated with three or more ADLs is less pronounced than in Table 5.6 where disease measures are disaggregated. While aggregating diseases simplifies the model, it does limit interpretability somewhat by combining conditions with different pathologies and treatment protocols.

Table 5.7. Mean Medicare Costs by Self-Reported Aggregate Conditions and ADL Counts

	Cancer		Heart Disease	
ADL Count	N (Unweighted)	Cost ($)	N (Unweighted)	Cost ($)
0	6,542	4,491	12,584	4,670
1	1,519	7,090	3,519	7,293
2	820	7,662	1,915	7,901
3	517	9,828	1,147	11,249
4	386	13,351	985	12,482
5	361	15,891	920	12,246
6	221	23,061	546	21,923
Nursing home	1144	13,780	3,508	12,355

SOURCE: 1992–1998 MCBS

NOTES: 1. Observations are weighted by normalized annual cross-sectional weights (weights in each year sum to one). 2. All costs are in 1998 dollars.

Cost Regressions

We impute costs in the microsimulation by computing fitted values from cost regressions. The primary dependent variables used in the cost regressions are Medicare reimbursements and their components (Part A and Part B reimbursements), and total medical expenses.[5] The set of independent variables includes demographics such as age, sex, ethnicity, education, geography (region and urban residence), and death. Measures of physical health include self-reported health; ADL categories, including nursing home residence; self-reported disease indicators; and interactions of these measures.

The final regressions are based on weighted least squares rather than alternative approaches such as the two-part model or modified versions of it. The least squares method is robust to asymmetric and highly skewed errors, although there is a loss of efficiency compared to more complex estimators. The dependent variable in the model is total Medicare reimbursements. The contemporaneous set of independent variables is described above, with health status measures consisting of ADL categories (0, 1–2, 3+, nursing home), self-reported disease categories (binary measures of any cancer, heart disease, hypertension, stroke, arthritis, lung disease, Alzheimer's disease, and diabetes), and interactions of ADL categories and disease conditions.

Ever having smoked, residing in the Northeast, mortality, obesity, and physical health status (measured by number of ADLs and admission to nursing home) have considerable effects on expenditures. Individuals who die during the year have substantially higher medical expenses than survivors, which is consistent with the literature. Medical expenditures increase with age, until about age 85. Lower expenditures among the oldest elderly may reflect biological differences among those who have survived to that age as well as less aggressive medical treatment. We also find that costs increase substantially with ADLs, particularly with three or

[5] A panel of social science experts recommended not distinguishing the components of costs—e.g., inpatient, outpatient, and home health—because trends during the 1990s were so extreme, and this period is spanned by our data.

more. The interactions of ADLs and disease vary in magnitude and significance, both in this model and in other specifications.

We include two dummy variables in the regressions, for beneficiaries who have only Medicare Part A or Part B, but we turn them off when we project future Medicare expenditures, which may result in slight overestimates of aggregate federal Hospital Insurance (HI), Supplemental Medical Insurance (SMI), and Medicare expenditures and total health care expenditures. The final models are shown in Table 5.8.

Table 5.8. Least Squares Estimates from MCBS Cost Regressions

Characteristic	Total Expenditures ($)		Medicare expenditures ($)	
	Estimate	Std. Error	Estimate	Std. Error
Age 70 to 74	1,218	187	630	151
Age 75 to 79	1,165	200	605	166
Age 80 to 84	1,133	222	586	178
Age 85+	-146	267	-822	212
Male	605	150	370	118
Black	817	261	984	220
Hispanic	833	354	945	263
Death	6,101	569	9,870	470
Less than high school	-233	158	75	130
Some college	251	205	110	166
College or above	154	193	-149	138
Northeast	2,308	194	1,105	151
Midwest	-16	145	-165	117
West	883	208	526	177
Other (except South)	-2,603	398	-2,345	299
1-2 ADLs (no nursing home residency)	2,968	384	1,943	304
3+ ADLs (no nursing home residency)	10,819	1,037	7,776	874
Nursing home residency	31,929	1,063	6,985	627
Diabetes	1,559	194	1,052	167
Cancer	2,278	163	1,478	133
Heart disease	2,784	133	1,988	112
Stroke	1,287	288	932	251
Alzheimer's disease	570	577	548	500
Hypertension	981	110	651	92
Arthritis	555	111	303	93
Lung disease	1,453	211	898	181
Cancer and 1-2 ADLs	-736	413	-392	340
Cancer and 3+ ADLs	-183	857	-238	728
Cancer and Nursing home residency	-110	1,322	528	1,022
Heart disease and 1-2 ADLs	53	329	57	263
Heart disease and 3+ ADLs	272	765	46	672
Heart disease and nursing home residency	-1,114	901	-1,185	699
Stroke and 1-2 ADLs	621	638	237	483
Stroke and 3+ ADLs	1,964	965	1,650	839
Stroke and nursing home residency	190	968	-914	733
Arthritis and 1-2 ADLs	-581	956	-893	740
Arthritis and 3+ ADLs	-1,553	1,236	-2,192	1,042
Arthritis and nursing home residency	-141	963	-4,306	713
Hypertension and 1-2 ADLs	-440	315	-227	249
Hypertension and 3+ ADLs	-646	712	100	607
Hypertension and nursing home residency	-860	866	939	621
Diabetes and 1-2 ADLs	1,242	457	1,166	379
Diabetes and 3+ ADLs	3,482	873	2,677	747
Diabetes and nursing home residency	5,679	1,452	4,216	1,166
Lung and 1-2 ADLs	1,455	488	1,161	408
Lung and 3+ ADLs	1,559	1,046	1,112	921
Lung and nursing home residency	259	1,647	1,795	1,294
Alzheimer's and 1-2 ADLs	-776	353	-516	286
Alzheimer's and 3+ ADLs	-3,410	899	-2,158	759
Alzheimer's and nursing home residency	-2,806	887	-418	680
Ever smoked	756	134	773	106
Spline for BMI<20	-358	156	-337	136
Spline for 20<BMI<25	-56	45	-71	36
Spline for BMI>25	-101	25	-90	21
Medicare Part A only	-2,671	341	-2,774	182
Medicare Part B only	-3,267	741	-3,112	250
Constant	7,506	3,057	6,797	2,659

CHAPTER 6:

HEALTH STATUS

As noted previously, the microsimulation model consists of three main component models. First, parameter estimates from a health status transition model form the basis of individuals' health status forecasts from the moment they enter the simulation host data until they become deceased. Second, every year we rejuvenate the host data with age-65 individuals to ensure that the data remain representative of the entire population age 65 and older. We estimate a model to forecast trends in various measures of health status and adjust the relative weights of the rejuvenation sample in accordance with those trends. Third, we apply a model of health care expenditures as a function of demographic characteristics and health status to project Medicare and total health care expenditures. Chapter 5 explained the cost model; this chapter describes the health status transition model; and Chapter 7 describes the trend model for future Medicare entrants.

DATA

Our model of health status transition probabilities is based on the experiences of the respondents to the 1992–1998 MCBS. These data also form the basis of the microsimulation host data, so comparability is not an issue. We pool multiple MCBS waves and use 21,495 individuals for the transitions model. Other health surveys, such as the NHIS, may have larger samples, but would lack the comparability and provide only subsets of information on subsets of respondents. The MCBS sample is very heterogeneous with respect to health status: Distinguishing six health conditions with potentially 96 combinations (cells), the 21,495 MCBS respondents span almost the entire spectrum of conditions.

The sample selection criteria are as follows. Individuals must be at least 65 years old. This age minimum yields 28,371 respondents with a total of 72,774 interview years.[6] Our outcomes are annual transitions, so we keep only individuals who participated in two or more contiguous interview years, which leaves 21,534 individuals and 65,937 interview years. Finally, we drop all interviews of individuals with any missing value for any health measure of interest or for nursing home residency, which affects 39 individuals, and the final estimation sample consists of 21,495 individuals and 65,575 interview years. Each outcome (transition) requires two contiguous interview years (pairs); the 65,575 interview years translate into 44,160 interview pairs.

The health status measures of interest are described in detail in Chapter 7. Briefly, they include cancer (excluding skin cancer), heart disease, stroke, arthritis, Alzheimer's, lung disease, hypertension, diabetes, number of ADLs, and general health status. Table 6.1 presents prevalence and incidence rates in the MCBS estimation sample, including facility-based respondents but excluding respondents who were interviewed only once or had missing information, as of respondents' year of entry into the MCBS. (The tables in Chapter 4 present

[6] Health status information is only collected in the fall interview round, so for our purposes, there is only one interview per year.

prevalence rates by broad age categories in the community-based MCBS population, for comparison with NHIS prevalence rates.)

Table 6.1. Prevalence and Incidence of Select Conditions in the MCBS Estimation Sample

	Prevalence (%)			Incidence (%)		
Condition	**65+**	**65–69**	**70+**	**65+**	**65–69**	**70+**
Mortality				3.3	1.2	4.1
Cancer	18.6	15.2	19.9	1.8	1.5	1.9
Breast (women only)	6.5	6.4	6.5			
Prostate (men only)	5.2	3.4	6.0			
Uterus (women only)	3.0	3.1	3.0			
Colon	2.7	1.6	3.1			
Bladder	0.9	0.5	1.0			
Lung	0.8	0.8	0.8			
Kidney	0.4	0.4	0.4			
Throat	0.4	0.4	0.4			
Head	0.3	0.2	0.4			
Brain	0.2	0.2	0.2			
Other	4.3	3.4	4.7			
Heart disease	38.7	29.6	42.2	3.2	2.3	3.5
Angina pectoris/CHD	15.8	11.8	17.4			
Myocardial infarction	15.0	12.2	16.1			
Other	29.0	21.2	32.0			
Alzheimer's	4.9	1.1	6.4	1.2	0.3	1.5
Stroke	11.8	7.6	13.5	1.4	0.8	1.7
Diabetes	16.6	15.2	17.1	1.3	1.1	1.3
Hypertension	54.1	48.3	56.3	3.0	2.6	3.2
Lung[a]	14.1	13.0	14.6	1.4	0.9	1.5
Arthritis	56.3	47.6	59.7	4.4	4.4	4.4
Disability						
ADL≥1	30.8	21.2	34.5			
ADL≥3	10.3	5.6	12.1			
Nursing home	6.8	2.3	8.6	1.5	0.2	2.0

[a] Refers to lung disease, which excludes lung cancer.

Note that incidence rates increase sharply with age, particularly for heart disease, stroke, and entry into a (nursing home) facility.

Tables 6.2 to 6.9 show the distributions of age, sex, race, Hispanic ancestry, education, smoking (by sex), and marital status. All tabulations are based on the first interview year.

Table 6.2. Age Distribution, MCBS Estimation Sample

Age	Frequency	Percent
65–69	5,551	25.82
70–74	3,969	18.46
75–79	4,115	19.14
80–84	4,155	19.33
85–89	2,385	11.10
90–94	1,016	4.73
95–99	264	1.23
100+	40	0.19
Total	21,495	100.00

Table 6.3. Distribution of Sex, MCBS Estimation Sample

	Frequency	Percent
Female	12,914	60.08
Male	8,581	39.92
Total	21,495	100.00

Table 6.4. Distribution of Race, MCBS Estimation Sample

	Frequency	Percent
Native American	145	0.67
Asian, Pacific Islander	255	1.19
African American	1,985	9.23
White	19,110	88.0
Total	21,495	100.00

Table 6.5. Distribution of Hispanic Ancestry, MCBS Estimation Sample

	Frequency	Percent
Non-Hispanic	20,325	94.56
Hispanic	1,170	5.44
Total	21,945	100.00

Table 6.6. Distribution of Educational Attainment, MCBS Estimation Sample

	Frequency	Percent
High school dropout	9,248	43.02
High school graduate	6,575	30.59
Some college	2,892	13.45
College graduate	2,780	12.93
Total	21,495	100.00

Table 6.7. Distribution of Ever Smoked, by Sex, MCBS Estimation Sample

	Women		Men	
Ever Smoked?	Frequency	Percent	Frequency	Percent
No	7,876	60.99	1,789	20.85
Yes	5,038	39.01	6,792	79.15
Total	12,914	100.00	8,581	100.00

Table 6.8. Distribution of Currently Smoking, by Sex, MCBS Estimation Sample

	Women		Men	
Smoke Now?	Frequency	Percent	Frequency	Percent
No	11,552	90.17	7,171	84.20
Yes	1,259	9.83	1,346	15.80
Total	12,881	100.00	8,517	100.00

Table 6.9. Distribution of Marital Status, MCBS Estimation Sample

	Frequency	Percent
Single	10,730	49.92
Married	10,765	50.08
Total	16,839	100.00

MISSING DATA

As stated above, respondents with missing information on health conditions or facility residence were dropped from the estimation sample. For demographic characteristics, we attempted to fill in missing data from other waves and from CMS's program records on sex, date of birth, and race/ethnicity. Small numbers of missing variables remained. We imputed these variables randomly, in accordance with their MCBS sample distributions. For smoking, we imputed separately for men and women. All imputed variables were flagged with indicator variables. At first, we included these indicator variables in all transition models. However, very few turned out to be significant, indicating that variables were missing at random with respect to health transitions. We therefore omitted indicators for missing variables from our final model specifications.

RESULTS OF ESTIMATION

The health conditions that we use in our analysis are all self-reported. Health measures based on claims data might be expected to be more predictive of costs. In addition, medical costs vary by time beginning with the onset of a condition (duration) and tend to be particularly high in the final year of life. In order to account for these duration effects, it is necessary to know the year of onset of each condition. However, the results in this report are based on self-reported health conditions, with no information on the year of onset.

Mortality is an absorbing state. For cancer, cardiovascular disease, neurological disorders, diabetes, and hypertension, the MCBS questions were worded as "Did a doctor ever tell you that . . . ?" In other words, the question wordings define these conditions as absorbing states. Accordingly, we only model transitions into these states, without allowing for recovery. Similarly, we assume that residence in a facility is an absorbing state. We model transitions into

mortality, cancer, cardiovascular disease, neurological disorder, diabetes, hypertension, and facility residence as proportional hazard models:

$$\ln h_j(t) = \gamma' Age(t) + \beta X_j,$$

where

$\ln h_j$ = the log-hazard of onset of the j-th condition (including mortality and entry into a facility);

$Age(t)$ = a piecewise-linear spline transformation of age at time t (see below)

X_j = demographic characteristics and co-morbidities that affect the onset of condition j.

The baseline duration dependency is the dependency on respondent age, $\gamma' Age(t)$. The hazards of various conditions' onset are assumed to be linear with respect to age, with potentially different slopes before and after age 77, i.e., the baseline log-hazard is piecewise linear (also known as piecewise Gompertz or generalized Gompertz).[7]

The unit of observation is an interview pair. All explanatory covariates are measured with a one-year lag. Only individuals who, at the time of the first interview, did not suffer from a specific condition contribute to the model estimation. Therefore, the sample sizes for various health status transition models vary. For example, consider an individual who entered the MCBS in 1993 without cancer but with a heart condition. In 1994, his conditions are unchanged; in 1995, he is diagnosed with cancer; in 1996, his conditions are unchanged. This person starts out with a heart condition, so he does not contribute to the heart disease transition model. In 1993 and 1994, he is free of cancer, so he contributes two observations to the cancer transition model. The outcome in his first contribution (1993 to 1994) is zero, because he remained free of cancer; the outcome in his second contribution (1994 to 1995) is one, because he was diagnosed with cancer. He is out of the sample for subsequent years. We ignore the clustering that arises from the fact that the same individual may contribute more than once to a model.

Table 6.10 presents the results of estimation for hazard models of onset of cancer, heart disease, stroke, arthritis, Alzheimer's, lung disease, hypertension, diabetes and ADL1+ and ADL3+, and for entry into a facility. The coefficients on age indicate the baseline slopes on age. They are generally positive, i.e., the risks of onset of various conditions tend to increase with age. It may seem surprising that the age coefficients tend to be smaller after age 77 than before, i.e., that there is a deceleration in the risk pattern. Note, however, that this age pattern applies only to individuals without any co-morbidity. As individuals get older, they are more likely to suffer from various conditions, which have positive effects on the onset of other conditions. The net result is typically an acceleration of the log-hazard with age. We return to this issue below, in the discussion of mortality.

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[7] Formally, γ is a vector of two age slopes and $Age(t)$ is a spline transformation, $Age(t) = \begin{pmatrix} \min(A,77) \\ \max(0, A-77) \end{pmatrix}$, where A is (scalar) age at time t.

Table 6.10. Results of Health Transition Estimation (Log-Hazard Parameters)

	Cancer	Heart	Stroke	Alzheimer's	Hypertension	Diabetes	Lung	Arthritis	ADL1+	ADL3+	Nursing Home
Cancer			-0.1121						0.1234[b]	0.1763[b]	-0.0961
			(0.0906)						(0.0488)	(0.0670)	(0.0987)
Heart disease			0.2661[c]						0.1472[c]	0.2273[c]	-0.0597
			(0.0819)						(0.0400)	(0.0569)	(0.0817)
Stroke									0.2579[c]	0.5653[c]	0.4320[c]
									(0.0600)	(0.0712)	(0.0891)
Alzheimer's									-0.9946[c]	-0.4609[c]	1.1078[c]
									(0.1220)	(0.1275)	(0.1062)
Hypertension		0.4723[c]	0.3768[c]						0.2314[c]	0.2317[c]	-0.0946
		(0.0569)	(0.0858)						(0.0404)	(0.0603)	(0.0824)
Diabetes		0.2598[c]	0.2646[b]		0.[c]2399[c]				0.2121[c]	0.4148[c]	0.3063[c]
		(0.0726)	(0.1049)		(0.0832)				(0.0511)	(0.6713)	(0.0973)
Lung									0.4215[c]	0.2760[c]	0.0279
									(0.0519)	(0.0734)	(0.1122)
Arthritis									0.4987[c]	0.5052[c]	-0.1952[b]
									(0.0404)	(0.0613)	(0.0834)
ADL≥1											0.9173[c]
											(0.1027)
ADL≥3											0.4708[c]
											(0.0932)
Age<77 (spline)	0.0588[c]	0.0721[c]	0.0653[c]	0.1739[c]	0.0441[c]	0.0581[c]	0.0472[c]	0.0461[c]	0.0845[c]	0.0919[c]	0.1913[c]
	(0.0119)	(0.0096)	(0.0141)	(0.0197)	(0.0091)	(0.0142)	(0.0142)	(0.0072)	(0.0065)	(0.0102)	(0.0218)
Age>77 (spline)	-0.0102	0.0223[c]	0.0297[c]	0.0904[c]	0.0058	-0.0520[c]	0.0031	0.0059	0.0224[c]	0.0504[c]	0.0804[c]
	(0.0097)	(0.0067)	(0.0094)	(0.0083)	(0.0069)	(0.0135)	(0.0103)	(0.0061)	(0.0052)	(0.0061)	(0.0071)
Ever smoked	0.1498[a]	0.0394	0.2168[b]				0.7279[c]		0.2355[c]	0.1113[a]	0.0331
	(0.0842)	(0.0609)	(0.0934)				(0.0999)		(0.0436)	(0.0637)	(0.0869)
Under Weight		0.0963	0.3118[c]		-0.2386[c]	-0.2291[b]		-0.3483[c]	-0.0942[b]	0.1200[a]	0.4810[c]
		(0.0636)	(0.0889)		(0.0639)	(0.1100)		(0.0552)	(0.0462)	(0.0643)	(0.0813)
Obese		0.2431[c]	-0.1093		0.2911[c]	0.7130[c]		0.2642[c]	0.3953[c]	0.3575[c]	-0.2620[a]
		(0.0741)	(0.1274)		(0.0819)	(0.1038)		(0.0657)	(0.0524)	(0.0767)	(0.1514)
Male	0.3927[c]	0.1549[b]	0.0966	-0.0556	-0.2114[c]	0.0669	-0.0862	-0.2966[c]	-0.1929[c]	-0.1837[c]	-0.0886
	(0.0787)	(0.0601)	(0.0909)	(0.0950)	(0.0571)	(0.0889)	(0.0894)	(0.0477)	(0.0435)	(0.0661)	(0.0901)
Black	-0.0747	-0.0337	-0.0422	0.2375[a]	0.4792[c]	0.2300	-0.4448[b]	0.1371	0.0927	0.0807	-0.2033
	(0.1347)	(0.0959)	(0.1480)	(0.1437)	(0.1026)	(0.1450)	(0.1761)	(0.0847)	(0.0682)	(0.0949)	(0.1412)
Hispanic	-0.3389[a]	-0.1142	-0.2684	-0.2596	0.2647[b]	0.4259[b]	0.2825[a]	0.0025	0.1422	0.2047[a]	-1.0555[c]
	(0.1779)	(0.1200)	(0.1968)	(0.2247)	(0.1131)	(0.1668)	(0.1587)	(0.1048)	(0.0816)	(0.1136)	(0.2601)
HS dropout	0.0855	0.1188[b]	0.2182[b]	0.2413[b]	0.1280[b]	0.2045[b]	0.1869[b]	0.0963[a]	0.1470[c]	0.3008[c]	0.1550[a]
	(0.0809)	(0.0591)	(0.0856)	(0.0952)	(0.0606)	(0.0935)	(0.0888)	(0.0519)	(0.0421)	(0.0612)	(0.0830)
College graduate	0.1319	-0.0423	-0.2241	-0.0968	-0.1692[a]	0.1225	-0.2535[a]	0.0406	-0.1906[c]	-0.0251	-0.3503[c]
	(0.1060)	(0.0867)	(0.1398)	(0.0952)	(0.0885)	(0.1318)	(0.1395)	(00685)	(0.0641)	(0.0976)	(0.1496)
Constant	-8.4097[c]	-8.800[c]	-9.6897[c]	-17.8567[c]	-5.9379[c]	-8.5798[c]	-8.0812[c]	-5.5237[c]	-9.3354[c]	-11.359[c]	-19.496[c]
	(0.8705)	(0.6694)	(1.0448)	(1.4771)	(0.6617)	(1.0376)	(1.0440)	(0.5257)	(0.4788)	(0.7581)	(1.6485)
ln-L	-3799.23	-5402.80	-3185.27	-2577.32	-4877.19	-2861.02	-3047.76	-6277.41	-8813.26	-5403.68	-2775.01

NOTES: Asymptotic standard errors in parentheses;
Significance: [a]=10%; [b]=5%; [c]=1%.

Positive coefficients in Table 6.10 indicate a higher hazard and thus poorer health. The coefficients indicate shifts in the log-hazard and thus proportional shifts in the hazard or risk of onset. For example, hypertension increases the log-hazard of heart disease by 0.4723, i.e., it increases the risk of heart disease by 100*(exp[0.4723] – 1) = 60.4 percent. Table 6.11 provides the same information as Table 6.10, but with log-hazard coefficients transformed into percent changes in the various hazards (relative risks).

Table 6.11. Results of Health Transition Estimation (Relative Risks)

	Cancer	Heart	Stroke	Alzheimer's	Hypertension	Diabetes	Lung	Arthritis	ADL1+	ADL3+	Nursing home
Cancer			-10.60						13.13[b]	19.28[b]	-9.16
Heart disease			30.49[c]						15.86[c]	25.52[c]	-5.80
Stroke									29.42[c]	76.00[c]	54.03[c]
Alzheimer's									-63.01[c]	-36.93[c]	202.77[c]
Hypertension		60.37[c]	45.76[c]						26.04[c]	26.07[c]	-9.03
Diabetes		29.67[c]	30.29[b]		27.11[c]				23.63[c]	51.41[c]	35.84[c]
Lung									52.42[c]	31.78[c]	2.83
Arthritis									64.66[c]	65.73[c]	-17.73[b]
ADL≥1											150.25[c]
ADL≥3											60.13[c]
Ever smoked	16.16[a]	4.02	24.21[b]				107.07[c]		26.55[c]	11.77[a]	3.37
Under Weight		10.11	36.59[c]		-21.23[c]	-20.48[b]		-29.41[c]	-8.99[b]	12.75[a]	61.77[c]
Obese		27.52[c]	-10.35		33.79[c]	104.01[c]		30.24[c]	48.48[c]	42.98[c]	-23.05[a]
Male	48.10[c]	15.75[b]	10.14	-5.41	-19.05[c]	6.92	-8.26	-25.67[c]	-17.54[c]	-16.78[c]	-8.48
Black	-7.20	-3.31	-4.13	26.81[a]	61.48[c]	25.86	-35.90[b]	14.69	9.71	8.40	-18.40
Hispanic	-28.74[a]	-10.79	-23.54	-22.86	30.30[b]	53.10[b]	32.64[a]	0.25	15.28	22.72[a]	-65.20[c]
HS dropout	8.93	12.61[b]	24.38[b]	27.29[b]	13.66[b]	22.29[b]	20.55[b]	10.11[a]	15.84[c]	35.09[c]	16.77
College graduate	14.10	-4.14	-20.08	-9.23	-15.57[a]	13.03	-22.39[a]	4.14	-17.35[c]	-2.48	-29.55

NOTES: Asymptotic t-statistics in parentheses. Each entry shows the percentage change in the likelihood of developing the condition in the next year. For example, a person with diabetes has a 29.67% greater chance of getting heart disease in the next year than someone without diabetes.
Significance: [a]=10%; [b]=5%; [c]=1%.

All explanatory covariates are measured with a one-year lag, i.e., as of the first interview of the interview pair. Note the very powerful cross-effects of health conditions. Diabetes and hypertension significantly increase the risk of developing a heart condition. As explanatory covariates, ADLs are measured marginally. For example, the effect of three or more ADLs is found by adding up the coefficients of ADL≥1 and ADL≥3.

Men tend to have higher risks of cancer and heart disease than do women and lower risks of hypertension, arthritis, and disability.

Blacks and Hispanics have higher risks of hypertension. Hispanics also have higher risks of diabetes. Hispanics are far less likely than non-Hispanics to enter a facility, such as a nursing home.

Better-educated individuals tend to be in better health.

Having ever smoked increases the risk of cancer, stroke, lung disease, and disability, but not by very much and only marginally significantly for cancer. We do not control for current smoking behavior. Its effects often appeared counterintuitive, and we question the accuracy of respondents' reports. In addition, inclusion of current smoking behavior would require projections of future smoking behavior for the microsimulation model. We prefer to omit this covariate.

The model specifications do not control for household income. We are not convinced that the quality of income data in the MCBS is sufficiently high. Furthermore, the inclusion of income would require a projection model of income for the microsimulations. Thus, we prefer to omit it from the transition models.

In early model development stages, we included indicator variables that flag whether race, Hispanic ancestry, education, past smoking, and marital status were missing and imputed. Their coefficients were rarely significant, indicating that there is no systematic pattern in the missing rates of demographic covariates. We therefore need not include these indicator variables.

The estimates of Table 6.10 form the basis of the health status projection algorithms in the microsimulation model.

Table 6.12 shows the estimates of the hazard model of *mortality*. The first and second columns show log-hazard coefficients; the third shows percent changes in the mortality risk. These estimates are based on MCBS data. The MCBS may or may not capture all deaths, so the next subsection compares MCBS estimates to Vital Statistics (NCHS, 1992-1998).

Table 6.12. Results of Mortality Estimation (Log-Hazard Parameters and Relative Risks)

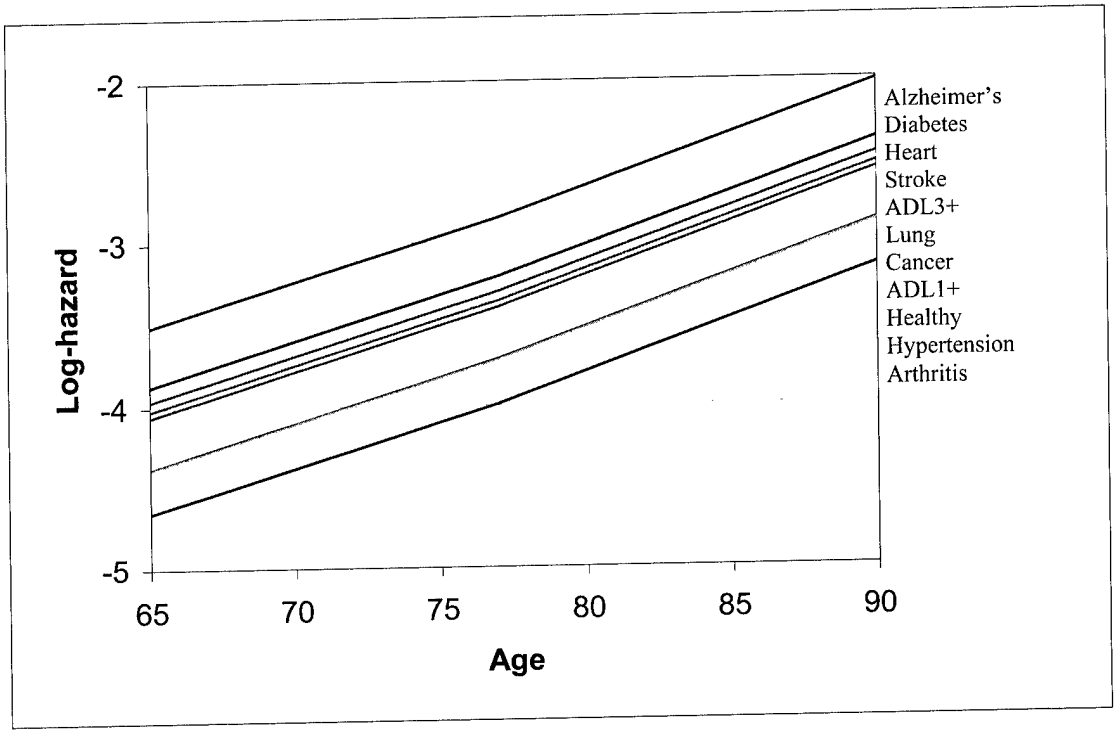
	Log-Hazard Coefficients		Percent Hazard Changes
	Male	Female	
Age<77	0.0547 [c]	0.0932 [c]	
	(0.0114)	(0.0130)	
Age>77	0.0641 [c]	0.0707 [c]	
	(0.0065)	(0.0051)	
Constant	-7.9263 [c]	-11.2608 [c]	
	(0.8371)	(0.9688)	
Cancer	0.3199 [c]		37.70 [c]
	(0.0499)		
Heart disease	0.4103 [c]		50.73 [c]
	(0.0450)		
Stroke	0.3785 [c]		46.01 [c]
	(0.0515)		
Alzheimer's	0.8654 [c]		137.60 [c]
	(0.0599)		
Diabetes	0.5044 [c]		65.60 [c]
	(0.0515)		
Lung	0.3557 [c]		42.72 [c]
	(0.0548)		
Arthritis	-0.2727 [c]		-23.87 [c]
	(0.0467)		
Hypertension	-0.0039		-0.39
	(0.0454)		
ADL≥1	0.2766 [c]		31.86 [c]
	(0.0551)		
ADL≥3	0.3711 [c]		44.93 [c]
	(0.0625)		
Ever smoked	0.1785 [c]		19.54 [c]
	(0.0519)		
Under weight	0.4428 [c]		55.71 [c]
	(0.0474)		
Obese	-0.0961		-9.16
	(0.0759)		
Black	0.0716		7.42
	(0.0760)		
Hispanic	-0.2753 [b]		-24.07 [b]
	(0.1112)		
High school dropout	0.1172 [b]		12.43 [b]
	(0.0463)		
College graduate	-0.2564 [c]		-22.62 [c]
	(0.0771)		
ln-L	-7511.37		

NOTES: Asymptotic t-statistics in parentheses;
Significance: [a]=10%; [b]=5%; [c]=1%.

As before, all explanatory covariates are measured with a one-year lag, i.e., as of the first interview of the interview pair. With the exception of arthritis and hypertension, all health conditions increase the risk of mortality.

Figure 6.1 illustrates the effects of morbidities on mortality risk for men.

Figure 6.1. Log-Hazard of Mortality for Men with Selected Health Conditions



The figure illustrates several features. First, the overall age pattern is increasing, i.e., older men face higher mortality risks. There is a kink in the age pattern at age 77. Before age 77, the log-hazard increases 0.0547 (about 5.5 percent) per year. After age 77, the increase is 0.0641 (about 6.4 percent) per year (see Table 6.12). Healthy individuals enjoy the second-lowest mortality risks. Cancer, heart disease, stroke, Alzheimer's, lung disease, and disability increasingly elevate mortality risks, whereas arthritis lowers mortality risks. The effects of these conditions are to shift the age pattern parallel to the baseline (healthy) pattern. This parallel shift is a consequence of the assumed functional form. A shift in the log-hazard translates into proportional or relative changes in the hazard.

Even when the log-hazard of mortality appears to decelerate at higher ages, the actual pattern for any one individual may well accelerate. For example, someone may be healthy at age 65 and experience the lowest mortality log-hazard. If this person contracts heart disease at age 70, for example, he moves from the baseline curve to the heart disease curve. If further complications develop, he moves to even higher curves. The implication is that many individuals experience accelerating mortality risks.

Table 6.12 also reports the effects of demographic factors. In light of large sex differences in mortality risks, we allowed for a full sex interaction in age. The interaction terms are jointly strongly significant. Controlling for all health conditions, there is no differential mortality risk by race, but Hispanic ancestry reduces mortality risks. Better-educated individuals tend to live

longer. Having ever smoked increases the risk of dying, even conditional on cancer and lung disease.

The model does not control for marital status, even though it is highly significant and strongly predictive of men's mortality risk (and both sexes' entry rates into facilities). The reason for its exclusion is that inclusion would require an auxiliary model of marital status in order to project future marital status for the microsimulation exercise. We intend to develop such a model in the next iteration, as we also did for the Model of Income in the Near Term (MINT) that we developed for the Social Security Administration.

The estimates of Table 6.12 form the basis of the mortality projection algorithms in the microsimulation model. A correction will apply, as explained below, but that correction is minuscule.

MORTALITY

The mortality estimates of Table 6.12 are based on survival probabilities in the MCBS. While the MCBS presumably represents the elderly U.S. population, it is not a priori clear whether the resulting mortality rates represent mortality rates among all American elderly. It may be, for example, that deceased individuals could not be located and were incorrectly classified as attrited, which would bias mortality estimates downward.

The MINT that we developed for the Social Security Administration corrected for underdetection of mortality. Its mortality model was based on the 1968–1993 Panel Study of Income Dynamics. We follow a similar procedure here.

The MCBS data are from 1992 to 1998, too short a time span to identify a longevity trend. We therefore compare the MCBS mortality data to cross-sectional 1998 Vital Statistics of the United States. We convert Vital Statistics life tables into mortality spells[8] and estimate very simple hazard models, by sex, which only depend on age. We wish to compare these estimates to similar estimates based on the MCBS. To that end, we impose the Vital Statistics coefficients on MCBS data and estimate differential coefficients. See Table 6.13.

[8] For example, the male life table for 1998 states that out of 77,547 men age 65, 68,375 (88.2 percent) will survive to age 70. Census data indicate that there were 4.4 million men age 65–70 in 1998. We combine this information and create two hazard spells, one for survivors and one for men who decease between their 65th and 70th birthdays. The first spell spans five years (age 65–70) and is open; it carries a weight of 0.882*4.4 million; the second also spans five years (age 65–70) but is closed; it carries a weight of 0.118*4.4 million. We do this for all age categories above age 65 and for both sexes.

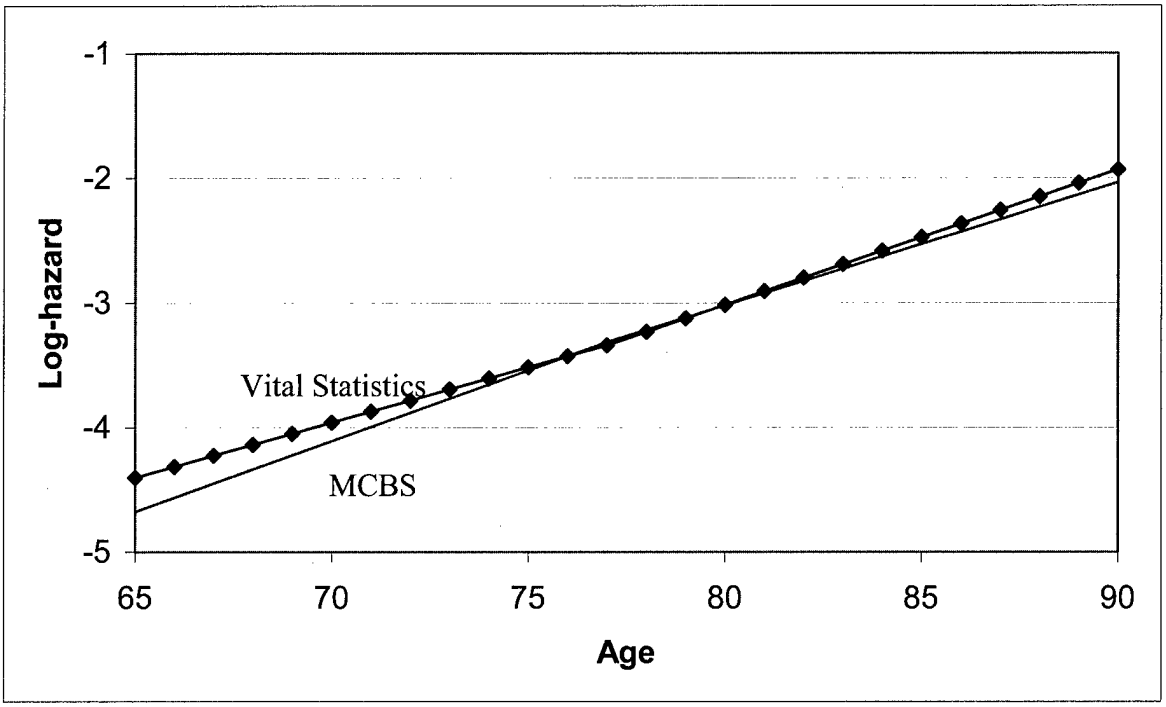
Table 6.13. Mortality Hazard Estimates from Two Soures

	Vital Statistics	MCBS (marginal coefficients)
Males:		
Constant	-9.2085 [c]	-0.1291
	(0.0161)	(0.8321)
Age<77	0.0819 [c]	0.0021
	(0.0002)	(0.0113)
Age>77	0.0971 [c]	-0.0098
	(0.0003)	(0.0065)
Females:		
Constant	-10.1469 [c]	-1.8924 [b]
	(0.0177)	(0.9520)
Age<77	0.0884 [c]	0.0249 [a]
	(0.0002)	(0.0128)
Age>77	0.1082 [c]	-0.0098 [b]
	(0.0003)	(0.0048)
ln-L	-13073761.48	-8012.46

NOTES: Asymptotic t-statistics in parentheses;
Significance: [a]=10%; [b]=5%; [c]=1%.

The Vital Statistics coefficients are very precisely estimated due to the huge underlying population size. For males, the MCBS estimates are not significantly different from Vital Statistics estimates. For females, there is a difference in the age slope under age 77. This difference is partially compensated by a seemingly very large intercept difference, but this intercept operates at birth. At age 65, the intercept difference is only –0.27 [=–1.8924+65*0.0249]. Figure 6.2 illustrates estimated age patterns for males based on Vital Statistics and the MCBS.

Figure 6.2. Log-Hazard of Male Mortality Based on Vital Statistics and the MCBS



The patterns are statistically and visually different, but are these differences substantial? A priori, it is impossible to tell; therefore, we anchor mortality estimates on Vital Statistics, which is done as follows. First, we estimate mortality models that control for health conditions and demographic characteristics using MCBS data. Second, for the purpose of projections, we correct for differences between Vital Statistics and the MCBS by subtracting the marginal coefficients of the MCBS (last column of Table 6.13) from model estimates. The resulting projection parameters lead to the same aggregate mortality rates as Vital Statistics parameters, with the advantage of differentiating mortality risk by health conditions and demographic characteristics. Our simulations showed very little difference between projection algorithms based on Vital Statistics or MCBS. Stated differently, the MCBS does an outstanding job identifying deceased respondents.

CHAPTER 7:

THE HEALTH STATUS OF FUTURE MEDICARE-ENTERING COHORTS

This subtask is designed to predict the health status of each of the future, entering cohorts of Medicare patients between the years 2001 and 2030. While it may be plausible to look simply at 65-year-olds in the year 2000 to predict the presence of chronic conditions and disability among 65-year-olds in 2001, such a procedure is likely to lead to misleading predictions for future entering cohorts, especially given the presence of well-known trends in the prevalence of disease and disability among all adult-age cohorts. If these trends continue, the health of 65-year-olds in 2030 is likely to look considerably different from the 65-year-olds today.

The measures of health status that we are most interested in here are the presence of seven of the most important, costly, and devastating chronic conditions that affflict the Medicare population: heart disease, hypertension, cerebrovascular disease, Alzheimer's disease or senile dementia, cancer, diabetes, and chronic obstructive pulmonary disease (COPD). In addition, we project future trends in the prevalence of disability among incoming Medicare cohorts. Our measure of disability focuses on self-reports by respondents regarding their ability to perform basic tasks of daily living, including bathing, dressing, and feeding themselves.

DATA

We use data from the NHIS, a large annual data set collected by the National Center for Health Statistics (NCHS). The NHIS is the right data set for our purpose because it is specifically designed to measure the population prevalence levels of a large number of chronic disease conditions and disabilities. Unlike another NCHS data set, the National Health and Nutrition Examination Survey (NHANES), the NHIS does not contain any physical exam or clinical data; health status is elicited from survey respondents using self-reports. However, unlike the NHANES, the NHIS is available for every year since 1957, contains large sample sizes, and used essentially the same questionnaire every year between 1982 and 1996. Because the survey instrument was redesigned in 1997, we use annual data between 1990 and 1996 to construct our projections. In addition, the NHIS contains extensive demographic and economic information about its respondents.

One drawback to the NHIS data set relates to its sampling scheme. Rather than asking all respondents about the presence or absence of a large number of disease conditions, the NHIS randomly divides the sample into six groups. Each respondent in a given group is asked about a different set of diseases than respondents in the other five groups. Therefore, no respondent is ever asked about the presence or absence of all of the chronic conditions considered by the NHIS. In fact, for a large subset of conditions, there is no overlap across the chronic condition questions list posed to each of the groups. However, the NHIS questionnaire also includes a list of questions regarding a small subset of chronic conditions that are posed to all respondents with some activity limitations.

Among the seven chronic conditions that we consider, questions regarding heart disease and hypertension are both posed to the same group of randomly selected respondents, whereas a

question on diabetes is posed to a different group. No comprehensive question on cancer is asked of all respondents. Instead, different groups of randomly selected respondents are asked about the most common types of cancer. Questions on breast and prostate cancer are posed to one group (the same group asked the question on diabetes), a question on lung cancer is posed to a second group, and a question on lung cancer is posed to yet a third group. We construct our estimates for total cancer incidence by summing over the incidence rates for each of the cancers separately.[9] Finally, a question regarding Alzheimer's disease is posed to NHIS respondents who report activity limitations.

Each year, several questions regarding disability status are posed to NHIS respondents who are between 25 and 69 years old. These disability questions include "Does any impairment or health problem now keep [you] from working at a job or business?" (*Work Limitation*), "[Are you] limited in any way in any activities because of an impairment or health problem?" (*Activity Limitation*), and "Because of any impairment or health problem, [do you] need the help of other persons with personal care needs, such as eating, bathing, dressing, or getting around the house?" (*Self-Care Limitation*). In addition, the NHIS includes a question on general health status (*General Health Status*), measured on a five-point Likert scale, that is posed to everyone in the data set. Unfortunately, none of these disability and health status questions map naturally to the ADL measures that are asked in the MCBS, so they cannot be used to directly infer changes in the prevalence profiles of people unable to perform one or more ADLs (ADL 1+), or three or more ADLs (ADL 3+).[10]

However, in 1995, the NHIS included an extensive supplement that posed a version of the ADL questions to its respondents.[11] Because the usual disability and health status questions were also posed to NHIS respondents in that year, we use these data to construct a map that predicts the presence of limitations in ADL from the usual NHIS questions on disability and health status. For the 1995 data, we estimate an ordered probit model that relates the total number of ADLs that respondents have difficulty performing to the Work Limitation, Activity Limitation, Self-Care Limitation, and General Health Status responses, in addition to a quadratic polynomial in age, and sex. The results of this model are presented in Table 7.1. The signs of the coefficients are consistent with common sense—older, sicker patients with more severe activity, work, or self-care limitations are more likely to report more limitations in performing ADLs. In turn, we use this model to predict ADL1+ and ADL3+ for each NHIS respondent in the years when these ADL questions were not asked. It is these predicted values that we use in our simulations of disability prevalence.

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[9] The NHIS questions for cancer are of the form "During the past 12 months, did anyone in the family have...?" so they are best interpreted as incidence rather than prevalence rates. This is in contrast to the NHIS questions for hypertension and heart disease, which are of the form "Has anyone in the family ever had...?" When we sum over the incidence of the various cancer types, we implicitly assume that the incidence of each cancer type is independent of the others. This is reasonable because it is rare for cancer to emerge simultaneously at two different primary sites.

[10] These are the indicators of disability status that our MCBS-based microsimulation model currently uses.

[11] There are some differences in the ADL questions posed in the 1995 NHIS supplement and in the MCBS. These differences lead to lower estimates of difficulty performing ADLs in the NHIS compared with the MCBS, as discussed in Chapter 4.

Table 7.1. Ordered Probit Model of Number of ADL Limitations

Variable	Estimate	t-Statistic
General Health[a]		
Very Good	.0329	0.425
Good	.205	2.91
Fair	.333	4.42
Poor	.692	8.96
Work Limitation[b]		
Limited in kind/amount of work	-.222	-2.70
Limited in other activities	-.111	-1.27
Activity Limitation[c]		
Limited in kind/amount of major activity	-.0414	-0.577
Limited in other activities	-.595	-5.94
Self-Care Limitation[d]		
Limited in performing routine needs	-1.29	-19.8
Not limited in performing personal care or routine needs	-2.00	-32.9
No Limitations	-2.19	-18.9
Age	.00735	0.581
Age squared	-.0000375	-0.289
Male	.0449	1.19
Cut Points		
Between 0 and 1 ADL	.166	.303
Between 1 and 2 ADL	.526	.303
Between 2 and 3 ADL	.778	.303
Between 3 and 4 ADL	1.01	.304
Between 4 and 5 ADL	1.22	.304
Between 5 and 6 ADL	1.75	.308
Log Likelihood	-3854.71	
Pseudo-R2	0.383	
N	51423	

[a]General Health Status = Excellent is the excluded category.
[b]Work Limitation = Unable to perform work is the excluded category
[c]Activity Limitation = Unable to perform major activity is the excluded category
[d]Self-Care Limitation = Unable to perform personal care needs is the excluded category

Finally, in addition to NHIS data, we need information on overall and cause-specific age-mortality profiles for each year between 1990 and 1996 inclusive. We obtain these data from the annual analysis of death certificate data, *Vital Statistics of the United States*, conducted by the NCHS (1992–1998). In the next section, we discuss how we combine these data to obtain disease prevalence projections for future incoming Medicare cohorts.

METHODS

Our strategy to predict the health status of future cohorts proceeds in four stages. First, for each chronic disease condition of interest, we use the NHIS data to obtain age-specific prevalence information. Though the NHIS has a large sample size overall, for some age cohorts the sample size is insufficient to produce noise-free estimates of low-prevalence diseases. Thus, we introduce a method to smooth the NHIS age-specific prevalence profiles, while at the same time accounting for trends in disease prevalence.

Second, we use a synthetic cohort-based procedure to obtain age-specific incidence rates from the smoothed prevalence profiles. In particular, we compare the prevalence of a disease in one year for one age cohort with the prevalence rate of that disease in the next year of data (where that cohort has aged by one year). Our procedure adjusts these raw prevalence differences to account for population and disease-specific death rates.

Third, we combine information from the most recent NHIS with our estimated age-specific incidence rates to obtain our predictions about the health status of the future incoming Medicare cohorts. For example, we add the prevalence of disease among 64-year-olds in 2000 to our estimated incidence rate for that disease among 64-year-olds to obtain our predictions about the 2001 class of 65-year-olds.

Fourth, we take our estimates of future prevalence among the entering cohort and use them to construct adjustments to the population weights of future entering cohorts with the various disease conditions.

Step 1: Smoothed Age-Specific Prevalence Rates

In order to describe the method we use to produce smooth age-specific prevalence functions—the overlap polynomial method[12]—it is helpful to introduce some notation. The NHIS is a repeated cross-section with hundreds of thousands of (say, N) observations. Each observation i, taken in $year_i$, consists of information about i's self-reports regarding disease conditions and disabilities, age (age_i), and other information (X_i). In the remainder of this section, we consider one disease condition, but extending the analysis to other conditions is straightforward. Let d_i indicate whether patient i has some chronic disease. We estimate the following logit model of disease prevalence using all the years of the NHIS data between 1990 and 1996 inclusive:

$$(7.1) \quad P[d_i = 1 | age_i, year_i] = \frac{1}{1+\exp(g_1(age_i;\beta_1)+g_2(year_i;\beta_2))}$$

The g functions allow the presence of disease to flexibly vary with the year of observation and the age cohort of the respondent. Age cohort enters the model through g_1, which is specified using an overlap polynomial:

[12] MaCurdy, Green, and Paarsch (1990) were the first to use this method in economics. Bhattacharya, Garber, and MaCurdy (1998) used this method to smooth cause-specific mortality profiles for the elderly.

$$(7.2)\quad g_1(age_i) \sum_{j=0}^{K}\left(\Phi\left(\frac{age_i - k_{j+1}}{\sigma_1}\right) \Phi\left(\frac{age_i - k_j}{\sigma_1}\right)\right)p_j(age_i;\beta_{1j})$$

where $p_j(age_i;\beta_{1j})$ $j = 0\ldots K+1$ are all n^{th}-order polynomials in age_i. The knots are $k_0\ldots k_{K+1}$, and σ_1 is a smoothing parameter, which in addition to n, are all fixed before estimation. We use first-degree polynomials. Although we experimented with higher-order polynomials, we find that they add to the costs of computation with no change in the final projections.

The properties of the overlap polynomial can best be appreciated when the smoothing parameters approach zero. When this is the case, $\Phi(.)$ reduces to an indicator function equal to zero if $age < k_j$ and one if $age \geq k_j$. Thus the first term of the sum, $\left(\Phi\left(\frac{age_i - k_1}{\sigma_1}\right) \Phi\left(\frac{age_i - k_0}{\sigma_1}\right)\right)p_0$, equals p_0 when $k_0 < age \leq k_1$, and zero otherwise. Thus between k_0 and k_1, the prevalence rate is given by p_0, which in turn depends on the parameters $\beta_{1,0}$. Similarly, between k_1 and k_2, the prevalence rate is determined by p_1; between k_2 and k_3, it is determined by p_2; and so on. Allowing positive values of the smoothing parameters eliminates the sharp discontinuity of the growth rates at the knots. In fact, one advantage of this overlap polynomial over traditional splines is that the function and all its derivatives are automatically continuous at the knots without imposing any parameter restrictions.[13]

In addition to an overlap polynomial for age, we also include another overlap polynomial, g_2, for year, to flexibly allow for changes in the age-prevalence relationship over time. Here, the knots are m_j, $j = 0\ldots M$, the smoothing constant is σ_2, and q_j are the polynomials. As before, experimentation led us to use first-order polynomials in year.[14]

$$(7.3)\quad g_2(year_i) \sum_{j=0}^{M}\left(\Phi\left(\frac{year_i - m_{j+1}}{\sigma_2}\right) \Phi\left(\frac{year_i - m_j}{\sigma_2}\right)\right)q_j(year_i;\beta_{2j})$$

Although 7.1 does not include any covariate information regarding i, such information can readily be incorporated into the analysis by replacing the equation with the following:

$$(7.1a)\quad P[d_i = 1|age_i, year_i, X_i] = \frac{1}{1+\exp\left(\left(g_1(age_i;\beta_1) + g_2(year_i;\beta_2)\right)X_i\right)}$$

This framework can also be adapted to allow for interactions between age and year effects:

$$(7.1b)\quad P[d_i = 1 \mid age_i, year_i, X_i] = \frac{1}{1 \quad \exp\left(\left(g_1 \quad g_2 + g_1 * g_2\right)X_i\right)}$$

---

[13] After some experimentation, we chose $k_0 = -\infty$, $k_1 = 25$, $k_2 = 35$, $k_3 = 45$, $k_4 = 55$, $k_5 = 65$, $k_6 = 75$, $k_7 = \infty$, and $\sigma_1 = 25$.

[14] After experimentation, we chose $m_0 = -\infty$, $m_1 = 91$, $m_2 = 93$, $m_3 = 95$, $m_4 = \infty$, and $\sigma_2 = 4$. In all our analyses, $year_i$ is entered as $year_i - 1900$.

The object of the maximum likelihood logit estimation is to obtain consistent estimates for β_1 and β_2—$\hat{\beta}_1$ and $\hat{\beta}_2$, respectively. In this version of our estimates, for the sake of simplicity, we use Equation 7.1 rather than Equation 7.1a or 7.1b. In future drafts, we will generalize our estimates to account for more interactions.

Using these estimates, it is easy to generate age-prevalence profiles representative for any particular year. Let $\rho_{t,a}$ be the disease prevalence among a-year-olds in year t. Then,

$$(7.4) \quad \rho_{t,a} = \frac{1}{N}\sum_i P\left[d_i \quad 1 \mid age_i \quad a, year_i = t; \hat{\beta}_1 \hat{\beta}_2\right]$$

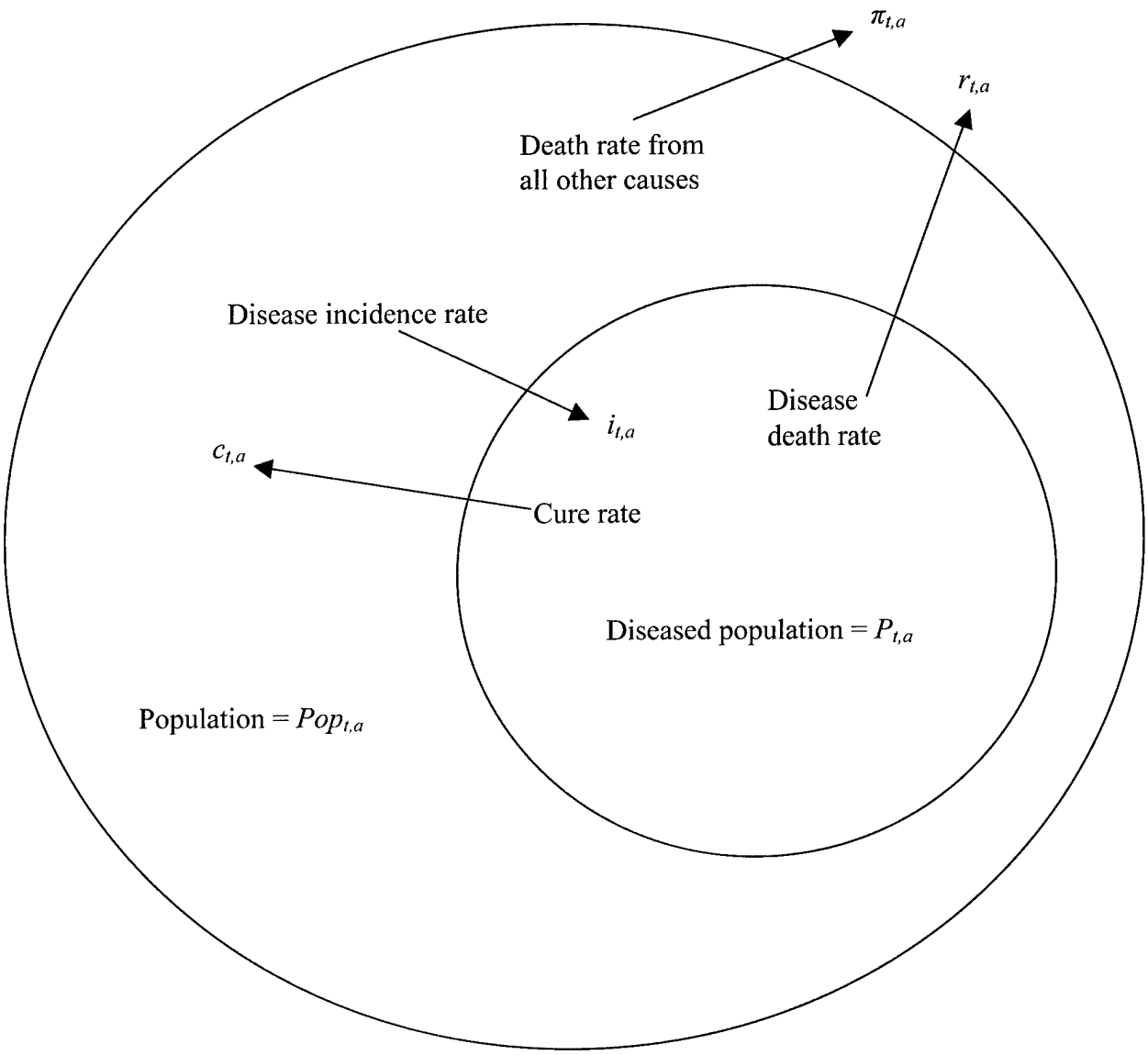
In the next section, we combine these estimates of disease prevalence with information on population and cause-specific death rates to derive yearly age-incidence curves.

Step 2: Estimating age-incidence profiles

The purpose of this section is to develop a simple model relating the prevalence of a disease in one period to its prevalence in the next period. We use a synthetic cohort approach to estimate an age-incidence profile for each disease from the prevalence estimates that we derive in the previous section. In the basic structure of our model, cohorts age from year to year and transition between health and disease. Because the NHIS is a nationally representative survey, $a - 1$-year-old respondents in year $t - 1$ are presumably drawn from the same population universe as a-year-olds in year t, except aged by one year. Broadly speaking, we derive our estimate of age-specific incidence rates by comparing successive prevalence rates.

In our model, the population transitions between health and illness from year to year. Figure 7.1 illustrates all the possible transitions for one disease. At time t, the size of the population who are age a is given by $Pop_{t,a}$. The size of the age a diseased population at time t is given by $P_{t,a} < Pop_{t,a}$. The $Pop_{t,a} - P_{t,a}$ patients without the disease condition, who are inside the large circle but outside the smaller circle, die from all other causes at a yearly rate given by $\pi_{t,a}$ and they develop the disease condition at the age- and year- specific incidence rate $i_{t,a}$. The $P_{t,a}$ patients inside the smaller circle die from the disease at a yearly rate given by $r_{t,a}$ and are cured at a rate given by $c_{t,a}$.

Figure 7.1. Population Transitions



Because there is no immigration of people into the population in Figure 7.1, the total size of the population age $a + 1$ at time $t + 1$ will equal the size of the population age a at time t, minus the people who die either from the disease condition or from other causes. The transition equation linking the population size of a given cohort from one year to the next is then given by:

(7.5) $Pop_{t+1,a+1} = Pop_{t,a} - (Pop_{t,a} - P_{t,a})\pi_{t,a} - P_{t,a}r_{t,a}$

Dividing through by $Pop_{t,a}$, we write Equation 7.5 in terms of the population age-specific prevalence of the disease, $\rho_{t,a}$, and the cohort growth rate $\gamma_{t,a}$:

$$(7.6) \quad \gamma_{t,a} \equiv \frac{Pop_{t+1,a+1}}{Pop_{t,a}} = (1 - \rho_{t,a})\pi_{t,a} - \rho_{t,a} r_{t,a}$$

We are interested in how the number of people with chronic diseases within a fixed cohort, who are age a at time t, changes as that cohort ages. This formula will allow us to relate incidence rates to changes in the prevalence rates that we calculate in Step 1, above. The number of people with chronic diseases in that cohort at $t + 1$ will equal all of those with the disease in the previous year save those who are cured or died, plus all the healthy people in the cohort who develop the disease. Therefore, the number of chronically ill within a fixed cohort evolves according to the following equation:

$$(7.7) \quad P_{t+1,a+1} = P_{t,a} + (Pop_{t,a} - P_{t,a}) i_{t,a} - P_{t,a} r_{t,a} - P_{t,a} c_{t,a}$$

Again, we divide through by $Pop_{t,a}$ to express Equation 7.7 in terms of population prevalence rates:

$$(7.8) \quad \gamma_{t,a} \rho_{t+1,a+1} = \rho_{t,a} + (1 - \rho_{t,a}) i_{t,a} - r_{t,a} - c_{t,a})$$

Finally, we rearrange Equation 7.8, solving for $i_{t,a}$ to write the age-incidence curve as a function of successive measurements of disease prevalence:

$$(7.9) \quad i_{t,a} = \frac{\gamma_{t,a} \rho_{t+1,a+1} - (1 - r_{t,a} - c_{t,a}) \rho_{t,a}}{1 - \rho_{t,a}}$$

We use information from equation 7.4 to generate estimates of disease prevalence rates, $\rho_{t+1,a+1}$ and $\rho_{t,a}$. We use information from Vital Statistics (NCHS, 2000) to generate information on disease-specific death rates $r_{t,a}$ and on overall death rates $1 - \gamma_{t,a}$. Data on disease-specific cure rates are not available from any single consistent source. Consequently, in our calculations, we assume that $c_{t,a} << r_{t,a}$. Because we are considering only chronic diseases with low cure rates, this assumption should not introduce too much error.[15]

Finally, taking linear combinations over t of $i_{t,a}$ generates age-incidence profiles that are representative for the period over which the linear combination is taken. Thus, in this framework it is easy to incorporate information about trends in disease or disability, at least to the extent that such trend evidence is present in the successive NHIS years that we use. Let the linear combination of age-incidence profile be i_a.

[15] Indeed, for some conditions, this is true by definition. For example, the NHIS asks respondents whether a doctor has ever told them that they had a heart attack. There is no cure for heart disease if it is defined in this way; once a doctor tells a respondent that he has had a heart attack, the respondent should always respond yes to this question.

Step 3: Projecting the health status of future Medicare-entering cohorts

Once the prevalence and incidence functions are calculated for each disease separately, we generate our projections for the health status of future entering cohorts of Medicare enrollees. The essential idea behind our projection is that for any given future year, we know how old the entering Medicare cohort is today. For example, writing in the year 2000, we know that the 65-year-olds of 2001 are currently 64 years old; $\rho_{2000,64}$ gives the prevalence of chronic disease among this cohort, and i_{64} gives the predicted proportion of those without disease in that cohort who will develop the disease between the ages of 64 and 65 (among those who are disease free at 64). The disease prevalence for 65-year-olds in 2001 is given by:[16]

$$(7.10)\quad \rho_{2001,65} = \frac{1}{\gamma_{2000,64}}\left(i_{64} \quad \rho_{2000,64}\left(1 \quad i_{64} - r_{2000,64}\right)\right)$$

Recursive application of this equation to different cohorts in the NHIS data yields predictions regarding the prevalence of this disease condition for the entering cohort of any future year y (as long as the cohort is alive at the time of the latest NHIS). Thus, for our disease prevalence estimates for 65-year-olds in 2002, we combine the disease prevalence numbers for 63-year-olds in 2000, which we observe directly, with our incidence estimates:

$$(7.11)\quad \begin{aligned} \rho_{2001,64} &= \frac{1}{\gamma_{2000,63}}\left(i_{63} \quad \rho_{2000,63}\left(1 \quad i_{63} - r_{2000,63}\right)\right) \\ \rho_{2002,65} &= \frac{1}{\gamma_{2000,64}}\left(i_{64} \quad \rho_{2001,64}\left(1 \quad i_{64} - r_{2000,64}\right)\right) \end{aligned}$$

Similarly, our projections for the year 2003 start with the disease prevalence of 62-year-olds in 2000, and recursively apply the incidence rates i_{62}, i_{63}, and i_{64} in three applications. By starting with progressively younger cohorts, and applying the recursion formula more times, we generate projections of disease prevalence for each year between 2001 and 2030. In principle, this method could be used to project disease prevalence for any future year, as long as the group of people who will be 65 in that year are alive today.[17]

Step 4: Constructing population weight adjustments from prevalence projections

The three steps we have heretofore described allow us to construct projections of future disease prevalence one disease at a time. While such univariate projections are independently

[16] For simplicity of exposition, the formula uses prevalence and incidence formulae based upon the 2000 NHIS. The actual calculation for the 2001 entering cohort starts with prevalence estimates for 60-year-olds in 1996, and uses the predicted incidence formulae for 61-, 62-, 63-, 64-, and 65-year-olds to generate the predicted 2001 prevalence. We do not use the 1997 and 1998 NHIS because the survey instrument changed in 1997, and it is not clear that the data before the change are directly comparable with the data after the change.

[17] As we mention in footnote 16, the discussion in the main text maintains the existence of the 2000 NHIS. Because the latest NHIS year we use is 1996, we start with disease prevalence rates of the 60-year-olds from that year to construct our year 2001 projections. Similarly, we use 59-year-olds from that year to construct our year 2002 projections, and so on.

interesting, they are insufficient for a project focused on predicting future Medicare expenditures. Elderly patients can have more than one chronic disease, and it is simply untrue that medical expenditures on a patient with two chronic diseases will equal the sum of expenditures on two patients, each with one chronic disease. Thus, in order to construct plausible estimates of total future Medicare expenditures, we need some estimate of the frequency with which chronic diseases jointly occur, as well as their frequency in isolation. This frequency distribution over the joint occurrence of chronic diseases can then easily be converted into predicted population weights for the incoming Medicare cohorts. Our purpose in this section is to describe the methodology we use to infer this joint frequency distribution.

As we mention above, in this report we focus on seven of the most-expensive-to-treat chronic disease conditions that afflict the elderly, in addition to a measure of disability. The disease conditions include heart disease, hypertension, cerebrovascular disease, Alzheimer's disease, cancer, diabetes, and COPD. For the purpose of this section we define a set of index variables $d_i^* = \{d_i^{*1}, d_i^{*2}, ...d_i^{*8}\}$, where the superscript indexes over each of the seven diseases and disability conditions, and i indexes over each member of some future Medicare incoming cohort. We redefine $d_i = \{d_i^1, d_i^2, ...d_i^8\}$ to be a set of indicator variables such that $d_i^j \quad 1(d_i^{*j} \quad 0) \; \forall j$, where $1(.)$ is the indicator function.[18] The analysis up to now allows us to estimate $\rho \{\rho_{65}^1 \quad P[d^1 = 1], \rho_{65}^2 \quad P[d^2 \quad 1], ...\rho_{65}^8 \quad P[d^8 = 1]\}$, but does not allow us to infer $P[d^1, d^2, ...d^8]$.

The critical missing ingredient is information on the joint incidence of these seven conditions and of disability in the population of interest. In principle, incoming Medicare cohorts can have 2^8 or 256 different combinations of our chronic diseases. In practice, however, many cells are likely to be sparsely populated. For example, fortunately few unlucky people are in the cell where $d^j \quad 1 \; \forall j = 1...8$, i.e., have all eight conditions. The most densely populated cells tend to be those where $d^j \prod_{j \neq k} (1 \quad d^j) = 1$ for some $j = 1...8$; that is, those cells the inhabitants of which have exactly one chronic condition. Also, some combinations of chronic conditions are quite important from an epidemiological and medical point of view, such as diabetes and heart disease, or hypertension and cerebrovascular disease.

Unfortunately, the NHIS does not allow us to derive an estimate of this joint distribution without further assumptions. As we describe in the Data section above, the particular sampling scheme used by the NHIS never asks respondents about the presence or absence of all disease conditions at the same time. The consequence of this data limitation is that using the NHIS we cannot derive the frequency of combined occurrence for some chronic conditions, including some important combinations (such as diabetes and heart disease).

To circumvent this difficulty, we augment our NHIS marginal prevalence estimates with information from Medicare recipients ages 65 to 70 years. We examine recipients in the 65–70-year age range because if we were to restrict the sample to just 65-year-olds our sample size in

[18] For the sake of notational simplicity in this section, we suppress the t subscript that reflects which future incoming Medicare cohort that i belongs to. For the same reason, we henceforth drop the i subscript as well.

the MCBS database would be too small to allow an accurate estimation of the correlation across the prevalence of disease conditions. Let the correlation matrix in d measured in this Medicare population be denoted by Σ. Because the disease variables are each dichotomous variables, for any j we have:

(7.12) $Var(d^j) = p_{65}^j(1-p_{65}^j)$.

Let $\Lambda = diag\left(\sqrt{Var(d^1)}, \sqrt{Var(d^2)}, \ldots \sqrt{Var(d^8)}\right)$. We assume that the joint distribution over d is generated by:

(7.13) $d^* \sim N(\Phi(\rho)\Lambda, \Lambda\Sigma\Lambda)$

Here, Φ^{-1} is the inverse of the standard normal cumulative density function applied element by element to the ρ vector. Both ρ and Λ are estimated from the NHIS data using the procedure we describe earlier, whereas Σ is estimated from an entirely different data source, MCBS, but is representative of the same population as the NHIS. The main attraction of the normality assumption is that it allows a significant reduction in the number of parameters we need to characterize the distribution over d. Instead of 256 numbers, one for each possible combination of d, we represent the distribution with 8 numbers for the univariate prevalence estimates and the $\binom{8}{2} = 28$ numbers for the correlation matrix. We show below that the normality assumption on the joint distribution of d^* allows us to recover information accurately on the first two moments of the d distribution.

Under the assumption represented by Equation 7.13, we can reproduce the observed marginal prevalence rates as the mean of the d distribution. To show this, we note first that all the diagonal elements of Σ are equal to one, since it is a correlation matrix. With a slight abuse of matrix notation, this implies that

(7.14) $diag(\Lambda\Sigma\Lambda) = diag(\Lambda) = diag\left(Var(d^1), Var(d^2), \ldots Var(d^8)\right)$

Given Equations 7.13 and 7.14, we have for each disease condition j that:

(7.15) $d^{*j} \sim N\left(\Phi^{-1}(p_{65}^j)\sqrt{\rho_{65}^j(1-\rho_{65}^j)}, \; p_{65}^j(1-\rho_{65}^j)\right)$

The population prevalence of disease j is given by:

(7.16) $P[d^j = 1] = P[d^{*j} > 0] = P\left[\dfrac{d^{*j} - \Phi^{-1}(p_{65}^j)\sqrt{p_{65}^j(1-\rho_{65}^j)}}{\sqrt{p_{65}^j(1-\rho_{65}^j)}} > -\Phi^{-1}(\rho_{65}^j)\right]$

Therefore,

(7.17) $P[d^j = 1] = 1 - \left(\Phi^{-1}(\rho_{65}^j)\right) = \left(\Phi^{-1}(p_{65}^j)\right) = \rho_{65}^j$.

In addition to the marginal probabilities of the d distribution, Equations 7.13 and 7.14 allow us to infer second-order moments, which are simple functions of the first moment—see Equation 7.12. In addition to these two moments, with the joint normality assumption over d^* we can now specify the joint probability distribution over d, $P[d^1, d^2, \ldots d^8]$, based upon known information:

$$(7.18)\quad P[d^1, d^2, \ldots d^8] = \int_{\frac{d^1-1}{d^1}}^{\frac{d^1}{1-d^1}} \cdots \int_{\frac{d^8-1}{d^8}}^{\frac{d^8}{1-d^8}} d\Phi^8\left(d^{1*}, d^{2*}, \ldots d^{8*}\right)$$

where $\Phi^8\left(d^{1*}, d^{2*}, \ldots d^{8*}\right)$ is the cumulative density function of the eight-variate normal distribution shown in Equation 7.13.

CHAPTER 8:
SCENARIOS

In this chapter, we show how we modified the FEM to simulate various scenarios involving likely breakthroughs identified by the expert panels. We compare the resulting disease prevalence and costs with those from the baseline scenario to evaluate the potential effectiveness of the breakthroughs.

After reviewing the list of breakthroughs identified by the expert panels with CMS, we agreed to model the following: telomerase inhibitors, cancer vaccines, diabetes prevention, compound that extends life span, changes in education, rise in Hispanic population, smoking, obesity, and an integrated cardiovascular disease scenario.

TELOMERASE INHIBITORS

Eligibility

Cancerous tumors can be divided into two categories: solid tumors, which affect organs, and liquid tumors, including leukemia and lymphomas, which affect blood cells. Solid tumors can be further divided into those that remain local and those that have resulted in disseminated disease. The expert panels predicted that, of the 50 percent of patients with solid tumors who have local disease, 50 percent would be eligible for telomerase inhibitor (TI), and of the 50 percent with disseminated disease, 10 percent would be eligible for TI.

Our cancer definition includes breast cancer, prostate cancer, uterine cancer, colon cancer, bladder cancer, lung cancer, kidney cancer, throat cancer, head cancer, brain cancer, and other cancers, including leukemia and lymphomas (see Table 8.1).

Table 8.1. Cancer Prevalence

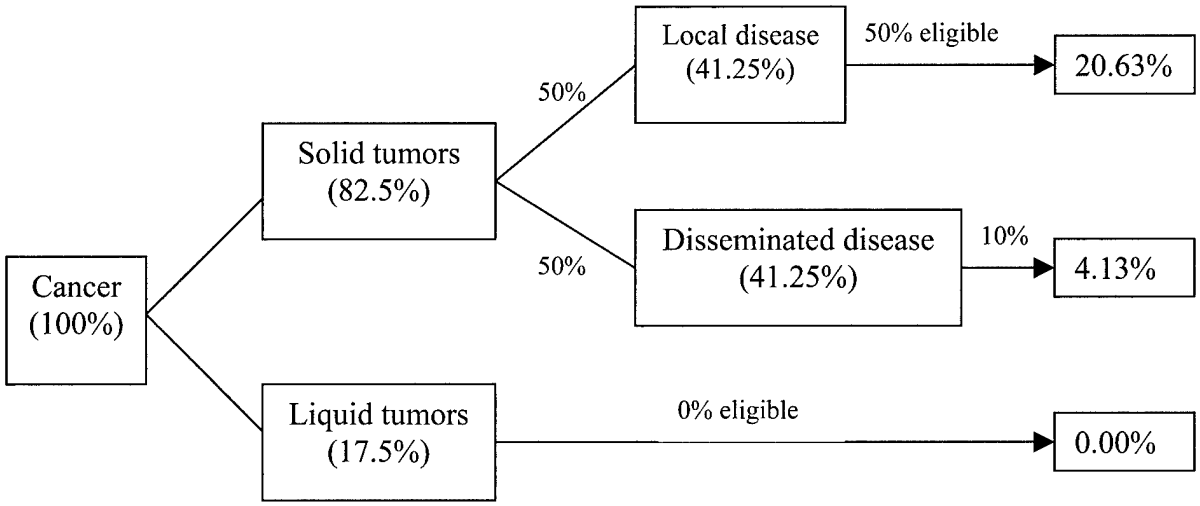
	MCBS Prevalence (65+) (%)
Cancer	17.7
Breast	6.5
Prostate	6.6
Uterus	2.9
Colon	2.5
Bladder	0.9
Lung	1.0
Kidney	0.3
Throat	0.5
Head	0.2
Brain	0.1
Other	3.1

The overall cancer prevalence is 17.7 percent, and the prevalence for other cancers is 3.1 percent. We use the prevalence of other cancers to approximate the prevalence for liquid tumors (3.1 percent), because we do not have separate cancer categories for leukemia and lymphomas in our estimation data set. Therefore, of all people with cancer, approximately 3.1 percent/17.7 percent, or 17.5 percent, have liquid tumors and 82.5 percent have solid tumors. As mentioned, approximately 50 percent of solid tumors are localized (41.25 percent of all cancers) and 50 percent represent disseminated disease (41.25 percent of all cancers). In our simulation, we cannot distinguish patients with different cancer types; therefore, we will randomly assign cancer patients to the three cancer categories according to their proportions, which are assumed to be constant over time in the course of simulation.

Among the three cancer categories, treatment rates vary: 50 percent of patients with local disease get treatment (41.25 percent * 50 percent = 20.63 percent of all cancers), 10 percent of patients with disseminated disease get treatment (41.25 percent * 10 percent = 4.13 percent), and no one with liquid tumors gets treatment (0 percent). Figure 8.1 illustrates the eligible population for TI.

In the first step of the simulation MCBS beneficiaries with cancer in the host data set are randomly assigned to those three cancer categories according to their prevalence in the MCBS population and are tracked until they die. Second, newly in- coming 65-year-olds and patients who newly acquire cancer in each following year are assigned to those three categories and tracked in the same way. Third, patients in each category are randomly chosen to receive the TI treatment according to the probability identified by the expert panels.

Figure 8.1. Eligible Population for TI



Effect

Of the patients who receive TI, 50 percent will be cured, and the other 50 percent will have a 25 percent prolongation of life (wide confidence interval: 10–50 percent). Patients who are cured by the treatment can get cancer again but will not be eligible for the treatment. For several reasons, the 25 percent prolongation of life is implemented by reducing the probability of death by 35 percent at all ages after the treatment takes effect. First, reducing the probability of death by 25 percent would increase life expectancy by less than 25 percent, as long as the probability of death is less than 25 percent; second, using the estimated probability of death for cancer patients from MCBS 1992–1998, we found that a 35 percent decrease in probability of death results in an approximately 25 percent increase in life expectancy. Treated patients are randomly assigned to these two categories. We also assume that TI takes effect immediately after patients start the treatment.

We assume that the treatment starts in the year 2002. The effect of TI on cancer prevalence is shown in Figure 8.2. Before 2002, cancer prevalence for both the baseline scenario and TI scenario is the same. After the TI treatment takes effect, cancer prevalence for the TI scenario is about 1.5 percentage points lower than that for the baseline scenario, which means that TI can reduce cancer prevalence by about 10 percent.

Figure 8.2. Cancer Prevalence Decline from TI

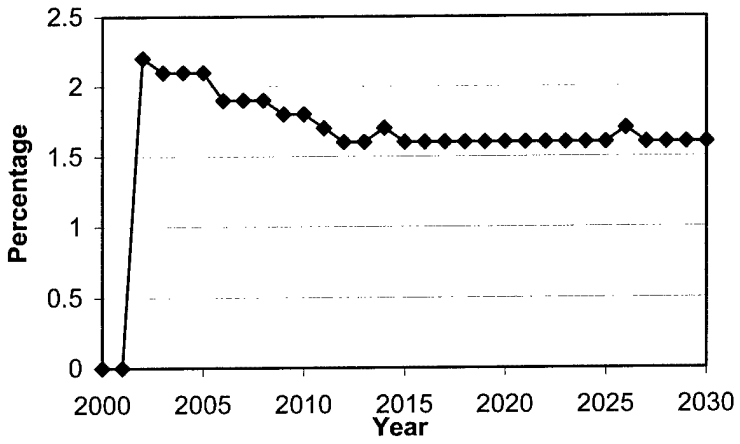
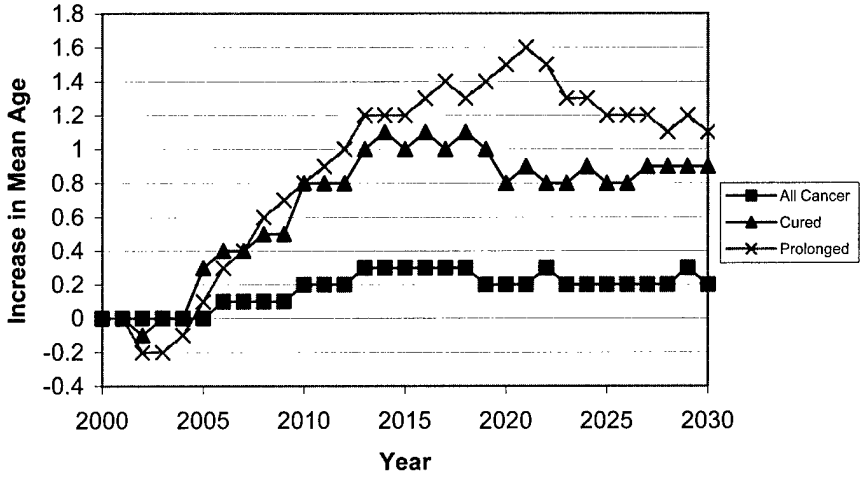


Figure 8.3 shows the effect of TI on life expectancy. Here we compare the average age for all cancer patients in the TI scenario, cancer patients who are cured by TI in the TI scenario and cancer patients whose lives are prolonged by TI in the TI scenario with the average age for all cancer patients in the baseline scenario. As expected, cancer patients who are cured and who have prolongation of life live the longest. The average age for the cured is less than that for the prolonged because a 25 percent increase in life expectancy for cancer patients has a larger effect on their life expectancy than does cancer itself.

Figure 8.3. Increase in Mean Age from TI for Cancer Patients



Cost

The cost for TI is similar to that for azidothymidine (AZT, also called zydovudine, an antiretroviral). The average wholesale price (AWP) for 100 100-mg capsules, a month's supply, is $176.95, and the patients must continue to take the medicine even after cancer is cured. Figure 8.4 shows the total treatment costs from 2000 to 2030, which increase almost linearly from $3 billion to $6 billion.

Figure 8.4. Total TI Treatment Costs

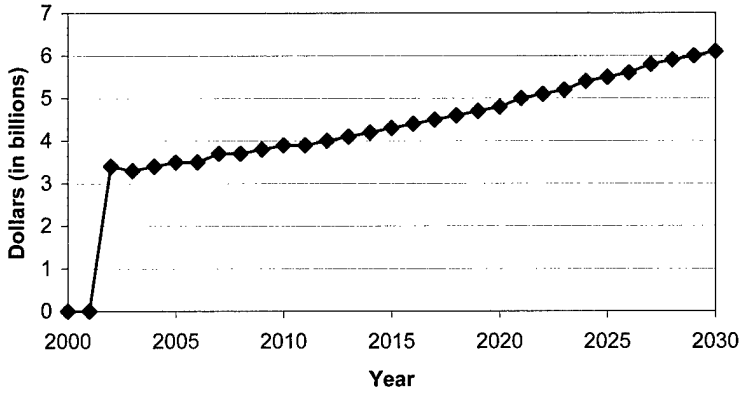


Figure 8.5 compares the Medicare expenditures for treating cancer patients in the TI scenario and the baseline scenario, and Figure 8.6 shows similar results for total expenditures. In both cases, the TI scenario has lower expenditures than the baseline scenario. This finding means the cost savings from curing cancer is greater than the costs of treatment for all cancer patients. Medicare incurs more savings because it does not pay the TI treatment costs.

Figure 8.5. Increase in Medicare Expenditures for Treating Cancer Patients with TI

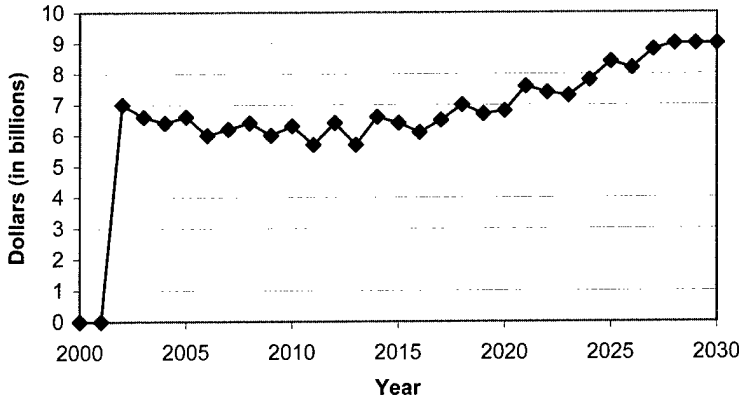
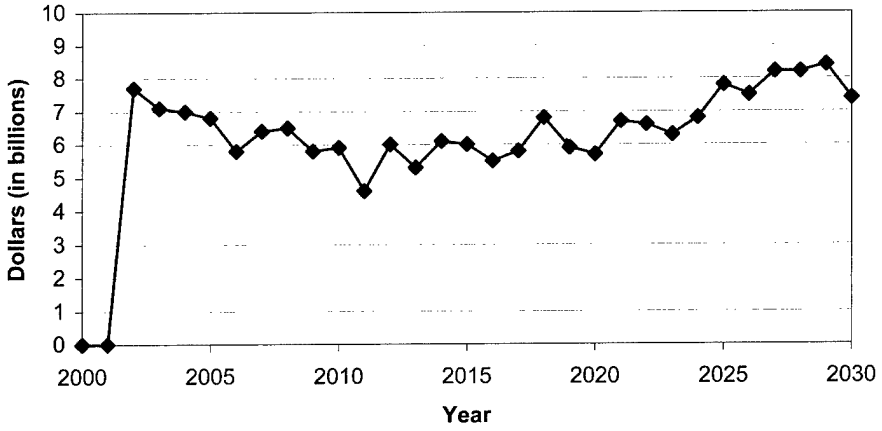
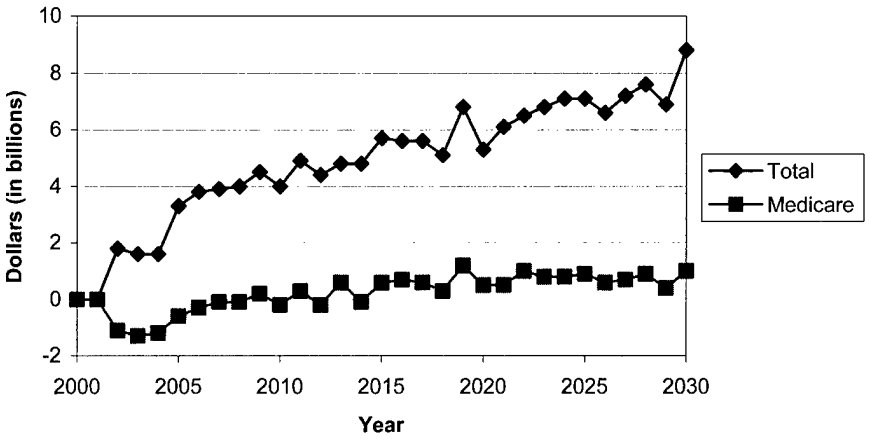


Figure 8.6. Increase in Total Expenditures for Treating Cancer Patients with TI



The effects of TI on Medicare and total expenditures are shown in Figure 8.7, where we show the extra costs due to TI treatment (TI scenario costs minus baseline scenario costs) for Medicare and total expenditures. The results show that the TI treatment increases total expenditures, but does not have much effect on Medicare expenditures. In the long run, TI treatment does not reduce Medicare expenditures, because TI treatment makes some cancer patients live longer by either curing their cancer or prolonging their lives.

Figure 8.7. Total and Medicare Cost Differentials Between Base and TI Scenarios



Discussion

TI would increase total expenditures for the elderly substantially, but would not, on its own, greatly affect Medicare spending. Cancer prevalence would be reduced quite a bit, and the people who get the treatment would do particularly well.

Some issues are worth considering. We do not have information about cancer type in our simulation; therefore, we use the 1998 proportions and assume they are constant over the course of the simulation. A more complicated scenario would examine the trends of those proportions from MCBS 1992–1998 and project forward. For example, we could use a probit model to estimate the probability of getting other cancers by demographic characteristics and health conditions. It is unlikely that these projections will have a material effect on what is shown here.

The expert panels provided both a mean (25 percent) and a range (10–50 percent) for the TI effect on prolongation of life. We modeled only the mean in our simulation. Because our conclusions are based on the aggregate statistics, modeling the variance explicitly may not change our results much.

The expert panels predict, "50 percent will have a 25 percent prolongation of life (wide confidence interval 10–50 percent)." We simulated the 25 percent prolongation of life by reducing the probability of death by 35 percent. The prolongation of life must be the result of improvement in health, but we failed to take into account this intermediate outcome, which may influence disease prevalence other than mortality.

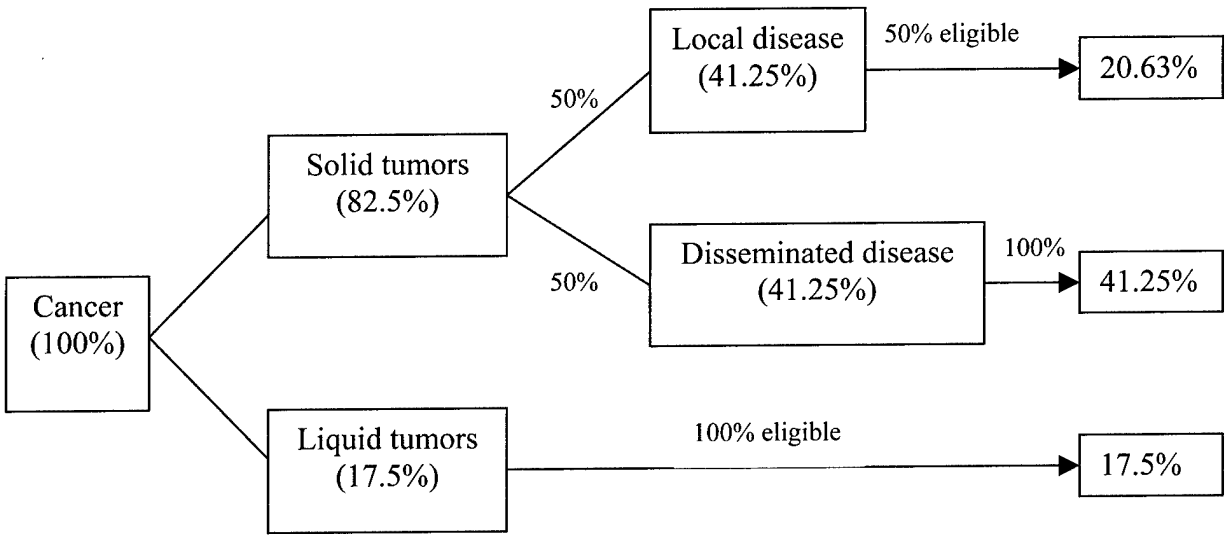
CANCER VACCINES

Eligibility

For this simulation, we used the same assumptions regarding cancer types and prevalence as were used for the TI simulation. Among the three cancer categories, treatment rates are assumed to vary by type: 50 percent of patients with local disease get treatment (41.25 percent * 50 percent = 20.63 percent of all cancer patients), 100 percent of patients with disseminated disease get treatment (41.25 percent * 100 percent = 41.25 percent of all cancer patients) and 100 percent with liquid tumors get treatment (17.5 percent). Figure 8.8 illustrates the eligible population for cancer vaccines (CV).

In the first step of the simulation, MCBS beneficiaries with cancer in the host data set are randomly assigned to those three cancer categories according to their prevalence in the MCBS population and are tracked until they die. Second, newly incoming 65-year-olds and patients who newly acquire cancer in each of the following years are assigned to those three categories and tracked in the same way. Third, patients in each category are randomly chosen to get the CV treatment, according to the probability identified by the expert panels.

Figure 8.8. Eligible Population for CV



Effect

Melanoma/renal cell carcinoma (kidney cancer) could be cured. However, we did not model melanoma (skin cancer) in our microsimulation. All other cancers could have a 25 percent

improvement in survival. We simulated cure of renal cell carcinoma by turning "cancer dummy" off for those who have kidney cancer and also get the CV. We randomly assign 0.32/17.73, or 1.8 percent, of cancer patients as kidney cancer carriers because we cannot distinguish patients with different cancer types. Patients who are cured by the vaccines can acquire cancer again but will not be eligible for retreatment.

A 25 percent boost in survival is brought about by reducing the probability of death by 25 percent at all ages every year after the treatment.

We assume that vaccines take effect immediately after patients start the treatment. We also assume that the treatment starts in the year 2002. The effect of vaccines on cancer prevalence is shown in Figure 8.9. Before 2002, cancer prevalence for both the baseline scenario and the CV scenario is the same. After the vaccines take effect, cancer prevalence for the CV scenario is about 0.7 percentage points higher than that for the baseline scenario, which means that vaccines actually increase cancer prevalence by about 5 percent. The reason is that vaccines cure only a small portion of cancer patients, which results in the initial decrease in cancer prevalence. For the majority of cancer patients who get the treatment, it only prolongs their lives and therefore increases cancer prevalence in the long run. The effect of prolongation on cancer prevalence increases over time, while the effect of curing cancer on cancer prevalence stays constant. After about three years, the prolongation effect exceeds the cure effect, and cancer prevalence for the CV scenario is greater than that for the baseline scenario.

Figure 8.9. Increase in Cancer Prevalence from CV

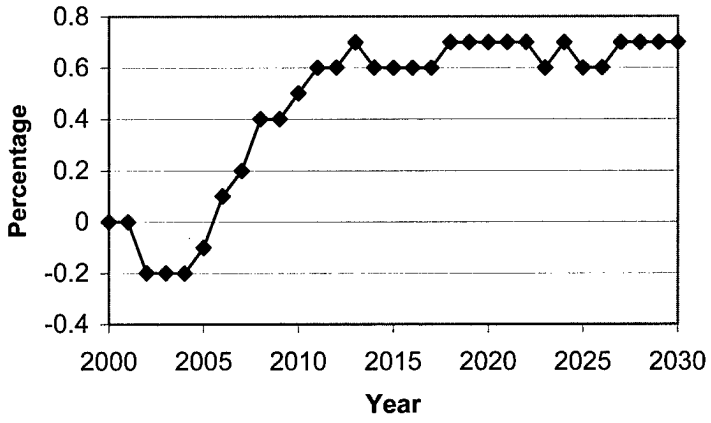
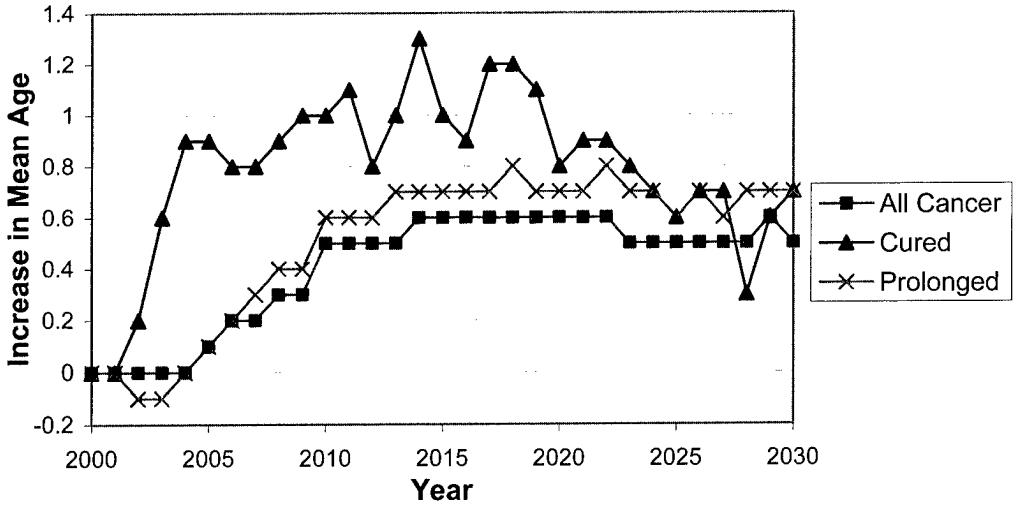


Figure 8.10 shows the effect of vaccines on life expectancy. Here we compare the average age for cancer patients in the CV scenario, cancer patients who get cured by vaccines in the CV scenario, and cancer patients whose lives are prolonged by vaccines in the CV scenario with average age for all cancer patients in the baseline scenario. Cancer patients who are cured by vaccines have slightly longer life expectancies than patients whose lives are prolonged from the treatment.

Figure 8.10. Increase in Mean Age from CV for Cancer Patients



Cost

The cost for vaccines may be two to three times more than that for hepatitis vaccine. The average wholesale price for three doses is $195.26, the total amount each patient needs to take. Figure 8.11 shows the total treatment costs from 2000 to 2030. In 2002, when the cancer vaccines were first introduced, all eligible Medicare patients got the treatment. However, after 2002, only newly entering eligible 65-year-olds got the treatment, which explains the sudden increase in CV treatment costs in 2002.

Figure 8.11. Total CV Treatment Costs

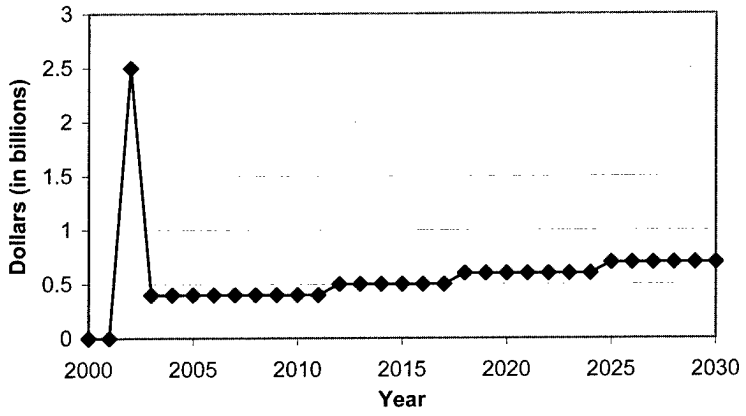


Figure 8.12 compares the Medicare expenditures of treating cancer patients in the CV scenario and the baseline scenario, and Figure 8.13 shows similar results for total expenditures. In both cases, the CV scenario has higher expenditures than the baseline scenario, because the portion of patients who are cured is small and the prevalence of cancer increases with the treatment.

Figure 8.12. Increase in Medicare Expenditures for Treating Cancer Patients with CV

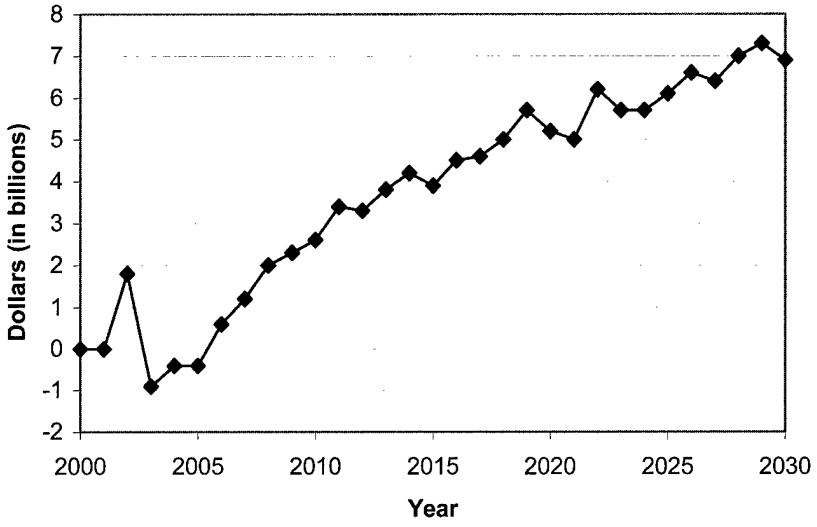
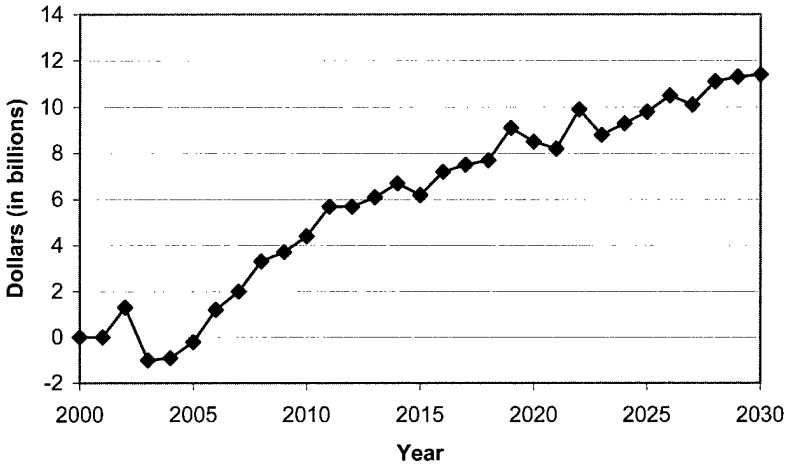
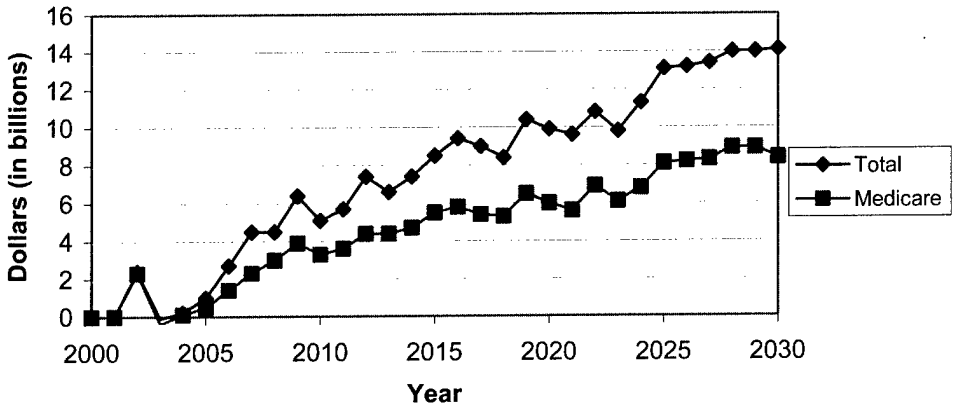


Figure 8.13. Increase in Total Expenditures for Treating Cancer Patients with CV



The effects of vaccines on Medicare expenditures are shown in Figure 8.14, where we show the extra costs due to vaccine treatment (CV costs minus baseline costs) for Medicare expenditures and total expenditures. The results show that the vaccine treatment increases both Medicare expenditures and total health care expenditures. The cost increase mainly comes from the prolongation of the lives of treated patients. The vaccine costs are relatively small and negligible.

Figure 8.14. Total and Medicare Cost Differentials Between Base and CV Scenarios



Discussion

Cancer vaccines have a large effect on prevalence but only a modest effect on costs. We did not model melanoma (skin cancer) in our microsimulation, although the vaccines could cure melanoma and therefore have a big effect on its prevalence and related expenditures. The expert panels predict, "cancers other than melanoma/renal cell carcinoma could have a 25 percent boost in survival." We simulated the 25 percent boost in survival by reducing the probability of death by 25 percent. The boost in survival must be the result of improvement in health, but we failed to take into account this intermediate outcome, which may influence disease prevalence differently than mortality.

DIABETES PREVENTION VIA INSULIN SENSITIZATION DRUGS

Eligibility

For the entire population, the expert panels predicted that "of the 80,000,000 obese, 10 percent [will] develop [type 2] diabetes mellitus (DM), and best targeting may be 30 percent, or 24,000,000," where obesity is defined as a body mass index (BMI) over 30. BMI is highly correlated with body fat and calculated by dividing a person's body weight in kilograms by the square of his or her height in meters. A BMI greater than 30 is widely accepted as an indication of obesity for adults. For the elderly population, we made the same assumption: that 30 percent of the obese elderly will get diabetes prevention (DP) treatment. .

Effect

We estimate that DP will result in 50 percent prevention of type 2 DM over five years. In the simulation, we reduce the probability of becoming diabetic by 50 percent over a ten-year period for obese elderly who get the treatment.

We assume that treatment takes effect immediately after patients start the treatment. We also assume that the treatment started in the year 2002. The effect of insulin sensitization drugs on diabetes prevalence is shown in Figure 8.15. Before 2002, diabetes prevalence for both the baseline scenario and DP scenario is the same. After the treatment takes effect, diabetes prevalence for the DP scenario is on average about 0.17 (range from 0.1 to 0.3) percentage points lower than that for the baseline scenario, which means that the treatment reduces diabetes prevalence by only about 1 percent.

Figure 8.15. Diabetes Prevalence Decline from DP

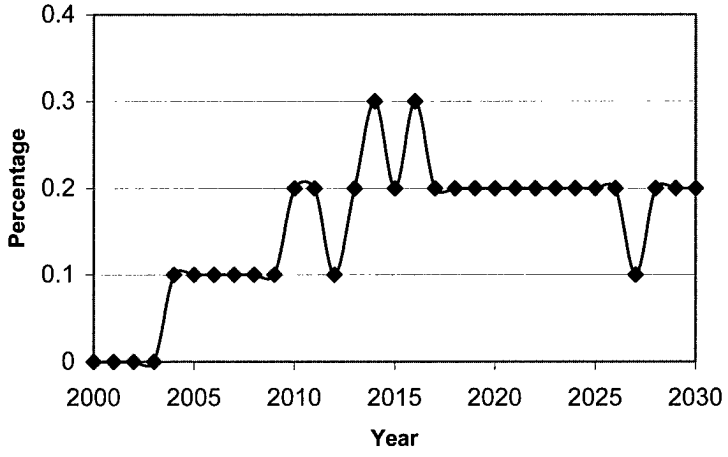
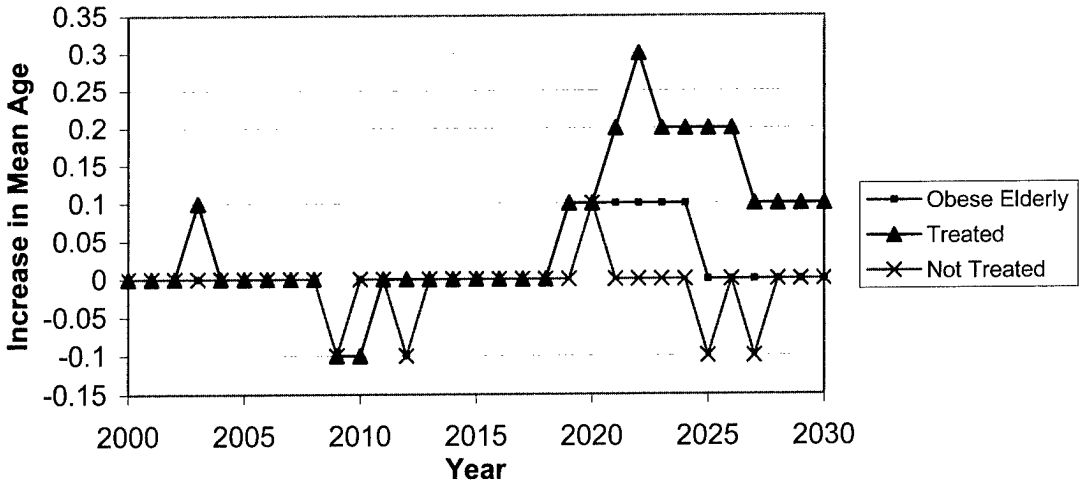


Figure 8.16 shows the effect of DP on life expectancy. Here, we compare the average age for all obese elderly in the DP scenario, obese elderly who get the treatment in the DP scenario, and obese elderly who do not get the treatment in the DP scenario with the average age for all obese elderly in the baseline scenario.

Figure 8.16. Increase in Mean Age from DP for Obese Elderly



Cost

The AWP for a month's supply of Roseglitazone is $108.25 (60 2mg tabs). Patients must continue to take the medicine until they die, regardless of the effects. Figure 8.17 shows the total DP treatment costs from 2000 to 2030.

Figure 8.17. Total Treatment Costs for Diabetes Prevention

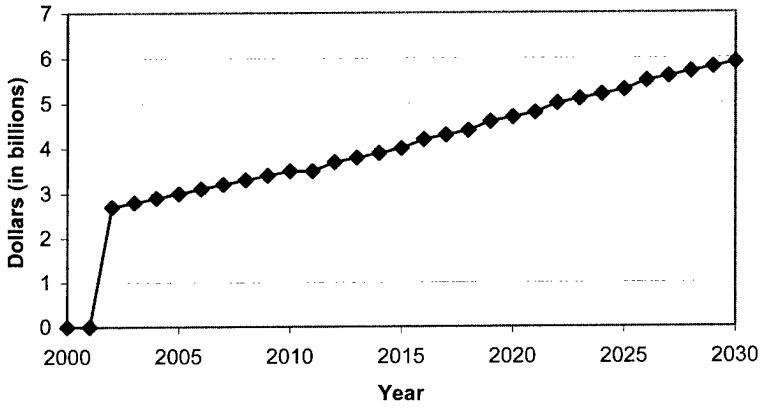


Figure 8.18 compares Medicare expenditures of treating obese elderly between DP scenario and baseline scenario, and Figure 8.19 shows similar results for total expenditures. The DP scenario has almost the same Medicare expenditures for treating obese elderly as the baseline scenario. The DP scenario has higher total expenditures for treating obese elderly than does the baseline scenario, but the difference is relatively small and close to the DP treatment costs (between $3 billion and $6 billion).

Figure 8.18. Cost Savings in Medicare Expenditures from Treating Obese Elderly with DP

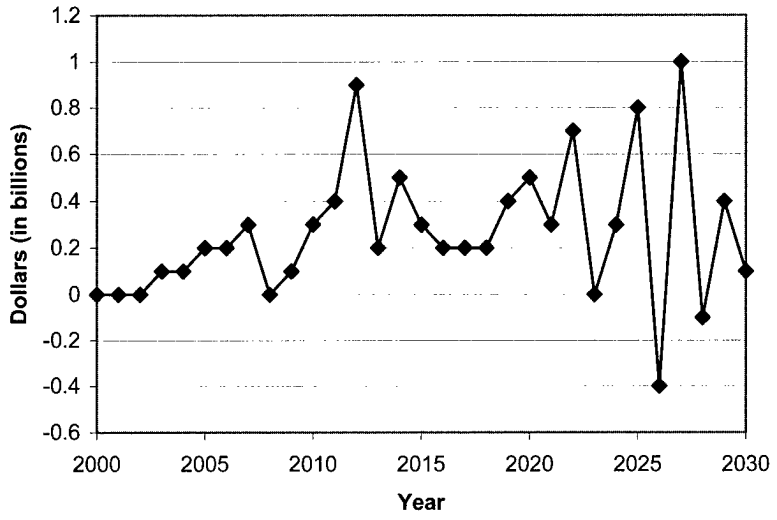
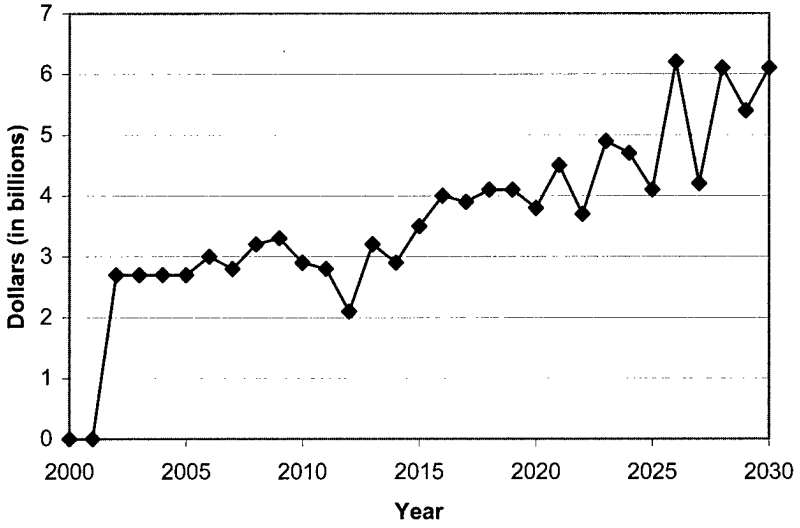
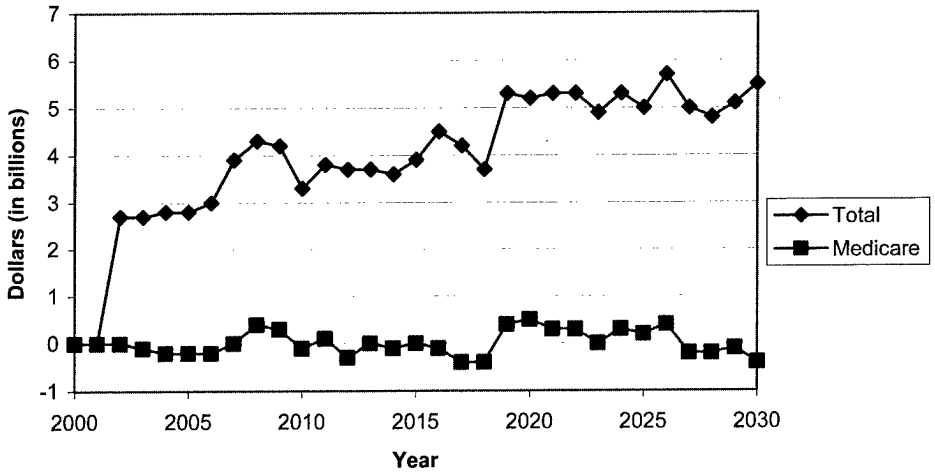


Figure 8.19. Increase in Total Expenditures from Treating Obese Elderly with DP



The effects of diabetes prevention on Medicare and total expenditures are shown in Figure 8.20, where we show the extra costs due to DP (DP scenario costs minus baseline costs) for Medicare and total expenditures. The results show that the DP treatment increases total expenditures but does not have much effect on Medicare expenditures. DP treatment slightly reduces Medicare expenditures in the short run, because Medicare does not pay for DP treatment costs. However, DP treatment does not reduce Medicare expenditures in the long run, because it makes some obese elderly live longer by reducing the probability of becoming diabetic.

Figure 8.20. Total and Medicare Cost Differentials between Base and DP Scenarios



Discussion

The insulin sensitization drugs can reduce the risk of developing type 2 diabetes by 50 percent over five years. We assume that all the diabetics in our simulation are type 2, and the insulin sensitization drugs can reduce the risk of becoming diabetic by 65 percent for ten years after starting the treatment. We also assume that only 30 percent of obese elderly will get the treatment, and no one gets the treatment before joining Medicare. We randomly choose 30 percent of all obese elderly to get the treatment in our simulation. Best "targeting" on those with the highest probability to develop diabetes might generate different results. For example, we can treat those 30 percent of obese elderly with the lowest survival probabilities predicted by our hazard models.

The effects are surprisingly small. The simulation results show that DP reduces diabetes prevalence by only about 0.17 percentage points, or 1 percent. In part, this finding reflects the relative size of the obese diabetic population. Our data indicate that among the obese elderly, diabetes prevalence is about 27 percent, and diabetes incidence is about 4 percent. Our diabetes prevalence is much higher than what expert panels believe (10 percent), but our prevalence applies only to individuals 65 and over, whereas the 10 percent figure provided by our expert panels applies to the entire population. For all individuals 65 and over, diabetes incidence is about 2.5 percent, of which about 0.9 percent are obese elderly. Three-twentieths (30 percent eligibility and 50 percent prevention) of 0.9 percent is about 0.17 percent.

COMPOUND THAT EXTENDS LIFE SPAN

Eligibility

Treatment with a compound that promises to extend the life span will start at an age of less than 65, because it may take more than 30 years to begin having a beneficial effect. Because our

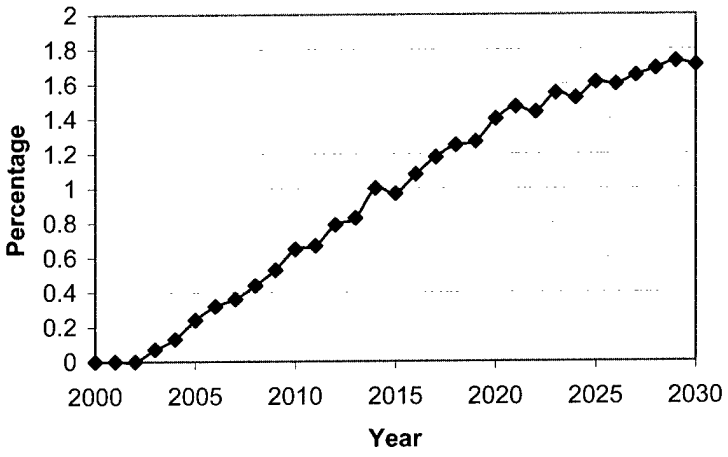
simulation extends only to 2030, we would see no beneficial effect; therefore, we assume that the treatment began to show an effect in 2002 or that the treatment was started in 1972 or earlier. We also assume that all elderly entering Medicare after 2002 have been subject to the treatment.

Effect

The treatment can extend life by 10 to 20 years with a health quality of those between 20 and 50 years of age. In part because our model can be applied only to individuals 65 and over and in part to simplify the analysis, we simulate here the effect of an extra 10 to 20 years of life by reducing the probability of death by 65 percent in each of the following years without altering projected health status. By doing so, we extend everyone's life by approximately 10 years on average. This estimate is based on the age-specific death rates from MCBS 1992–1998. However, the distribution is not uniform and people with better health and longer life expectancy benefit more from the treatment.

Figure 8.21 shows the comparison of death rates between the baseline and (Life-Extending) Compound scenarios. With more and more people in the elderly population living longer, the death rate decreases over time, although, as shown by the flattening of the curve, at a decreasing rate. In 2030, the death rate in the Compound scenario is 1.7 percentage points lower than that in the baseline scenario, a 41 percent decrease.

Figure 8.21. Death Rate Decline from Life-Extending Compound



As expected, extending life without improving in health results in higher disease prevalence; but the effects differ by disease (See Table 8.2).

Table 8.2. Disease Prevalence in 2030, Compound Scenario

Disease	Disease Prevalence for Base in 2030 (%)	Disease Prevalence for Compound in 2030 (%)
Cancer	16.4	22.3
Heart Disease	40.1	48.6
Stroke	8.5	12.0
Alzheimer's	2.0	2.9
Diabetes	18.4	23.0
Lung Disease	13.1	17.1
Arthritis	68.4	72.9
Hypertension	58.8	64.5
ADL1+	48.8	56.6
ADL3+	11.9	21.3
Nursing Home	5.0	6.7

Medicare and total expenditures increase dramatically due to the prolongation of life; and, whereas Medicare expenditures do not include the treatment costs, total expenditures do. On average, the prolongation of life will cost Medicare $51.8 billion per year, and total expenditures will go up by $88.1 billion per year from 2002 to 2030. (See Figures 8.22, 8.23, and 8.24).

Figure 8.22. Increase in Medicare Expenditures from Life-Extending Compound

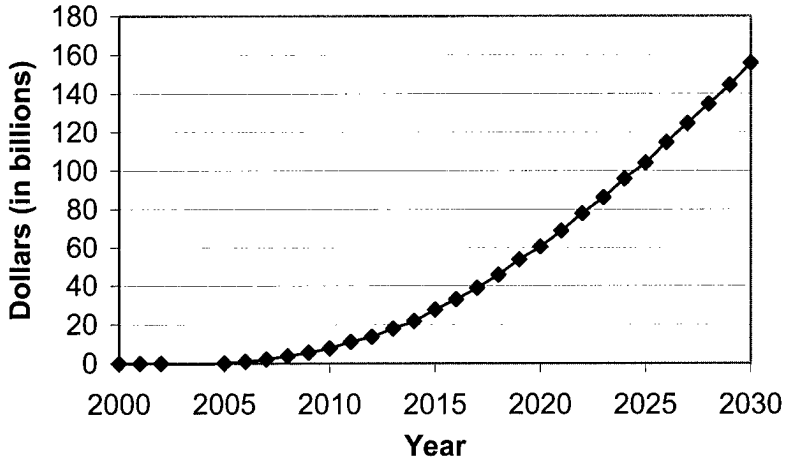
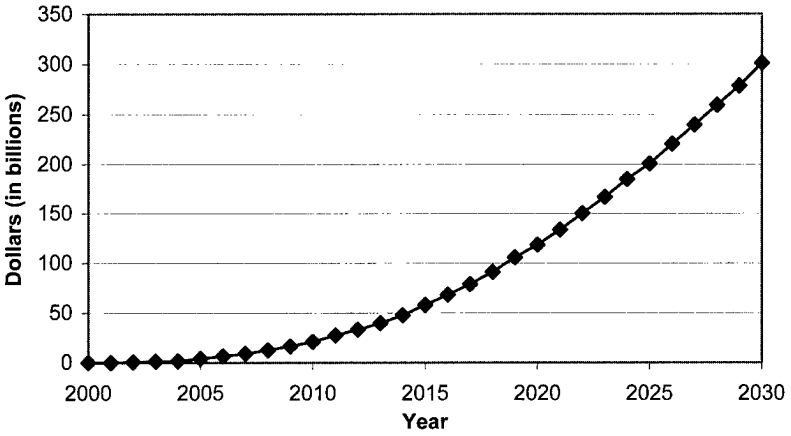


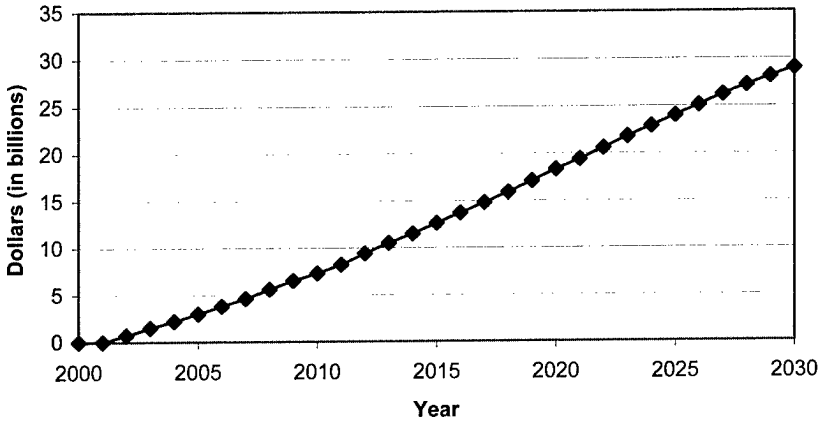
Figure 8.23. Increase in Total Expenditures from Life-Extending Compound



Cost

Like the cumulative costs of nutritional supplements, the cost for the compound will likely be approximately $1/day, but it may be more, if the Compound is a synthetic drug.

Figure 8.24. Total Treatment Costs for Life-Extending Compound



Discussion

Extending life expectancy has a tremendous effect on costs. This simulation assumes an increase in life expectancy but without a concomitant decrease in the intermediate health outcomes. The basic science surrounding this issue would suggest that such an improvement would also result in lower incidence of diseases such as cancer and cardiovascular disease. Here, the concept of active life expectancy—or compression of morbidity—might be more appropriate, wherein the hazard of disease is modeled not as a function of age but as a function of years remaining.

EDUCATION

Eligibility

We investigated two scenarios related to increasing educational attainment:

Educ-1: Assume that everyone entering Medicare after 2002 has a college degree or higher.

Educ-2: Assume the following transitions to higher educational attainment: those with less than a high school (HS) education → now have a HS education, HS → some college, some college → college, and college → graduate school (advanced degree). Transitions from less than HS to HS and from some college to college are effective in estimating both the survival probabilities and the costs. The transition from HS to some college is effective only in estimating the costs; and transition from college to graduate school is never effective because, in our model, we never distinguish between college graduates and graduate students (those who have not yet attained an advanced degree).

Effect

Improvement in overall education level for the entering 65-year-old cohort reduces the death rate. The difference in death rate gradually increases from zero to 0.6 percentage points as shown in Figure 8.25. In 2030, the death rate for Educ-1 is 0.57 percentage points lower than that for the baseline and the death rate for Educ-2 is 0.2 percentage points lower than that for the baseline. As expected, Educ-1 has a larger effect than Educ-2.

Figure 8.25. Death Rate Decline from Education Scenarios

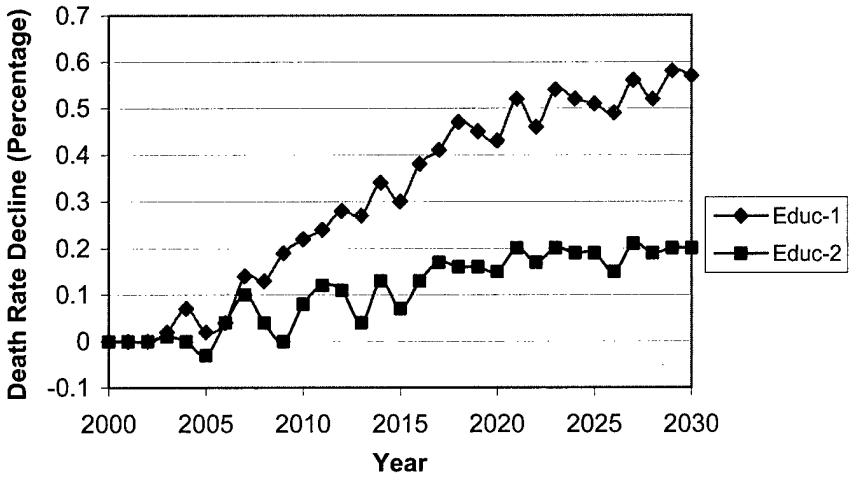


Table 8.3 shows the effect of improvement in educational attainment on disease prevalence. Prevalence of cancer, heart disease, stroke, diabetes, and arthritis in the Educ scenarios is higher than that in the baseline scenario. Prevalence for lung disease, hypertension (HTN), ADL1+, and nursing home residence in Educ scenarios is lower than that in the baseline scenario. Improvement in educational attainment has no significant effect on Alzheimer's disease prevalence. The pattern is similar to that for death rate, i.e., the absolute changes increase over time. The prevalence for Educ-2 always falls between the prevalence for baseline and the prevalence for Educ-1, except for ADL3+.

The changes in disease prevalence are the results of interaction between improvement in education and decrease in death rate. Improvement in education tends to reduce the disease prevalence while decrease in death rate increases disease prevalence.

Table 8.3. Disease Prevalence in 2030, Education Scenarios

Disease	Prevalence for Base (%)	Prevalence for Educ-1 (%)	Prevalence for Educ-2 (%)
Cancer	16.4	18.5	16.8
Heart Disease	40.1	41.2	40.2
Stroke	8.5	8.6	8.6
Alzheimer's	2.0	1.9	2.0
Diabetes	18.4	19.7	18.6
Lung Disease	13.1	12.9	13.0
Arthritis	68.4	70.0	68.5
HTN	58.8	57.6	58.3
ADL1+	48.8	47.3	45.7
ADL3+	11.9	12.5	9.9
Nursing Home	5.0	4.7	4.9

In the long run, improvement in education results in higher Medicare and total expenditures, as shown in Figures 8.26 and 8.27. In 2030, the differences in Medicare expenditures between Educ-1, Educ-2, and baseline are $8.6 and $1.5 billion, respectively. The differences in total expenditures between Educ-1, Educ-2, and baseline are $45.4 and $17.4 billion, respectively. However, the costs for improvement in education are difficult to estimate because it is difficult to determine how much of the estimated costs should be attributed to improvement in health.

Figure 8.26. Increase in Medicare Expenditures from Educ Scenarios

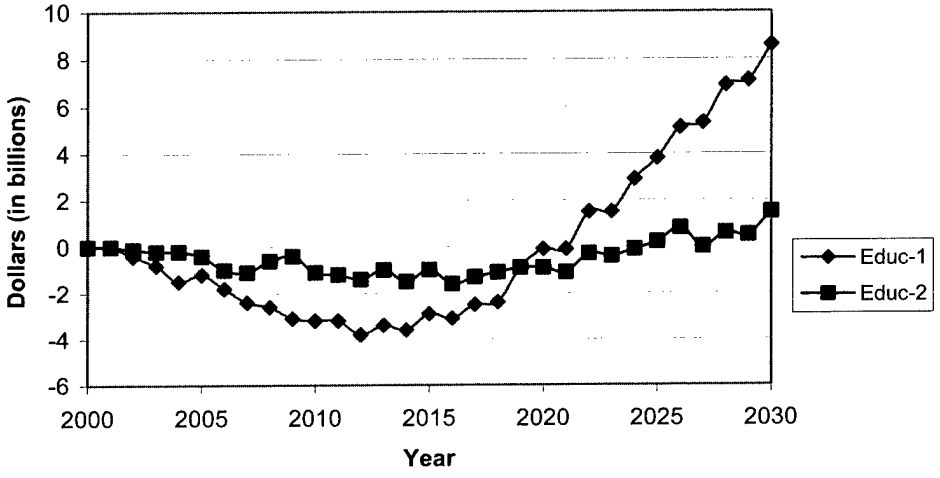
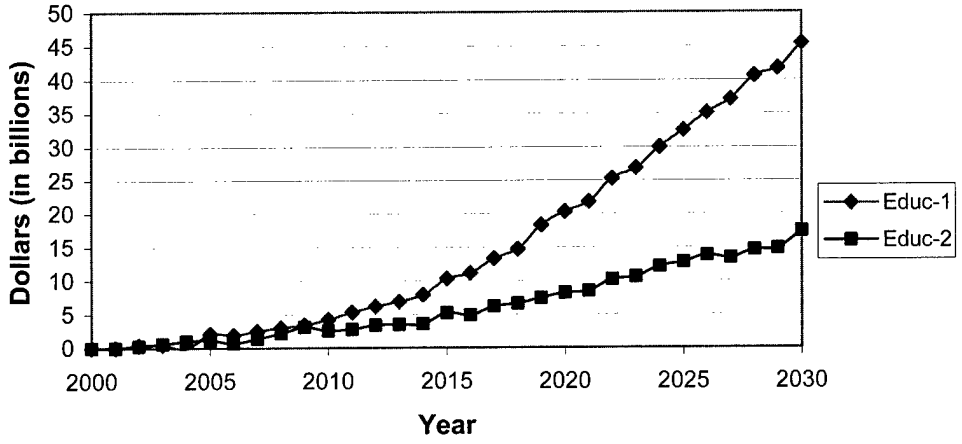


Figure 8.27. Increase in Total Expenditures from Educ Scenarios



Discussion

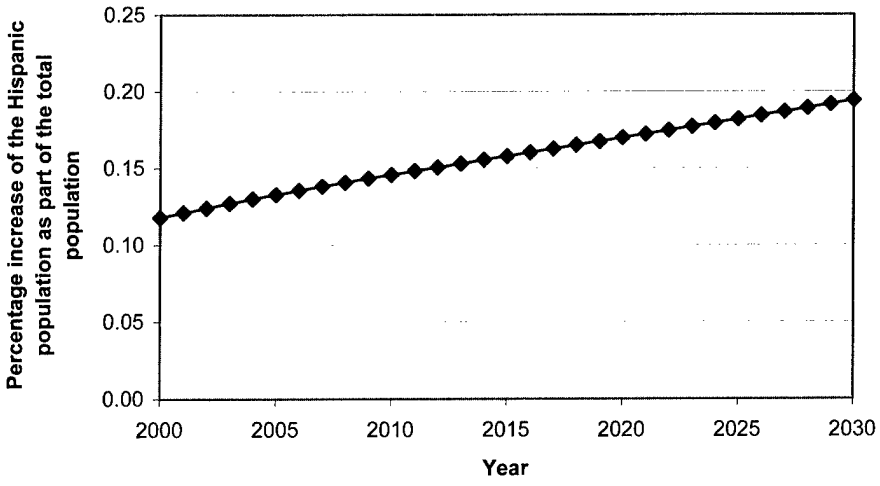
Neither of the educational scenarios is very realistic, but they serve several purposes. First, they demonstrate how FEM incorporates information about possible future changes in education level and projects their effects on health status, Medicare expenditures, and total health care costs. Second, these two scenarios provide us some sense of the magnitude of those effects. If these two extreme scenarios have only minor effects on health status and costs, then more realistic assumptions are even less likely to have significant effects.

RISE IN HISPANIC POPULATION

Eligibility

The proportion of the total U.S. population that is Hispanic has been increasing over time. Figure 8.28 shows the Hispanic population as a percentage of the total population from 2000 to 2030 using data from the Census's population projection. This percentage increases from about 11 percent to 19 percent over the next 30 years. We incorporate this trend by increasing the weights of Hispanic elderly in the simulation such that the proportion of the population that is Hispanic grows as predicted by the Census. By doing so, we can preserve other demographic characteristics, such as the health status and disease conditions of the Hispanic population, in the course of the simulation.

Figure 8.28. Hispanic Population Growth



Effect

Our scenario in which the Hispanic population increases (HISP) results in a higher death rate in the long run, as shown in Figure 8.29. HISP also results in higher prevalence of heart disease, diabetes, arthritis, hypertension (HTN), ADL1+, and ADL3+, and a lower prevalence of cancer, stroke, lung disease, and nursing home residence. HISP has no significant effect on the prevalence for Alzheimer's. Table 8.4 shows the comparison of disease prevalence between baseline and HISP scenarios. Figures 8.30 and 8.31 show the comparisons for both Medicare expenditures and total expenditures, from which we can see that HISP only slightly increases expenditures.

Figure 8.29. Increase in Death Rate Under HISP Scenario

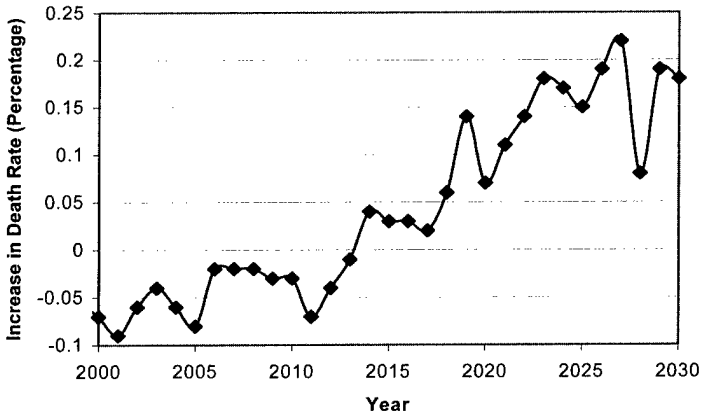


Table 8.4. Disease Prevalence in 2030, Hispanic Scenario

Disease	Disease Prevalence for Base in 2030 (%)	Disease Prevalence for HISP in 2030 (%)
Cancer	16.4	16.0
Heart Disease	40.1	40.4
Stroke	8.5	8.4
Alzheimer's	2.0	2.0
Diabetes	18.4	20.0
Lung Disease	13.1	12.9
Arthritis	68.4	69.0
HTN	58.8	60.7
ADL1+	48.8	50.5
ADL3+	11.9	13.7
Nursing Home	5.0	4.7

Figure 8.30. Increase in Medicare Expenditures Under HISP Scenario

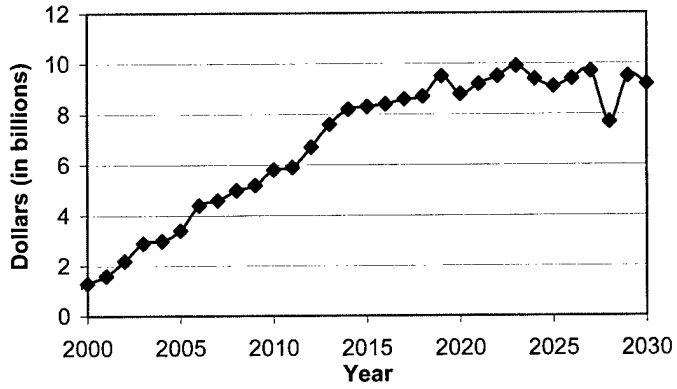
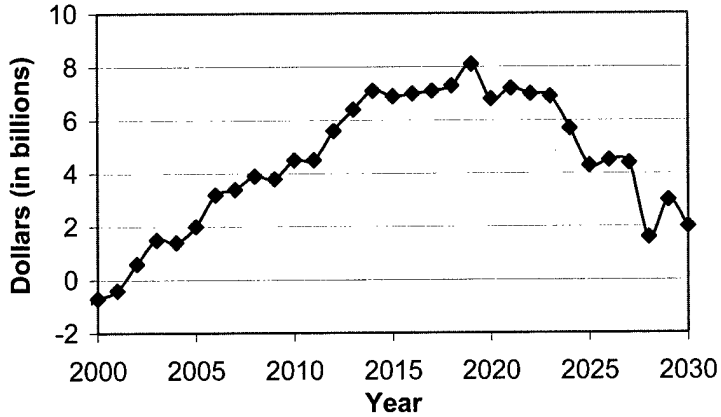


Figure 8.31. Increase in Total Expenditures Under HISP Scenario



Discussion

In the simulation, we implicitly assume that the future Hispanic population will have socioeconomic, demographic, and other characteristics similar to those of the current Hispanic population. If it does not, then the rise in Hispanic population could have very different effects from those shown above.

SMOKING

Eligibility

For this simulation, we assume that no one entering Medicare after 2002 ever smoked.

Effect

No smoking among entering 65-year-olds reduces the overall death rate. The difference in death rates between the baseline and the no-smoking scenario gradually increases from zero and stabilizes at about 0.3 percentage points as shown in Figure 8.32. The average death rate throughout the period 2000-2030 is 0.18 percentage points lower than that in 2002, or it decreases by 4.3 percent.

Figure 8.32. Death Rate Decline Under Smoke Scenario

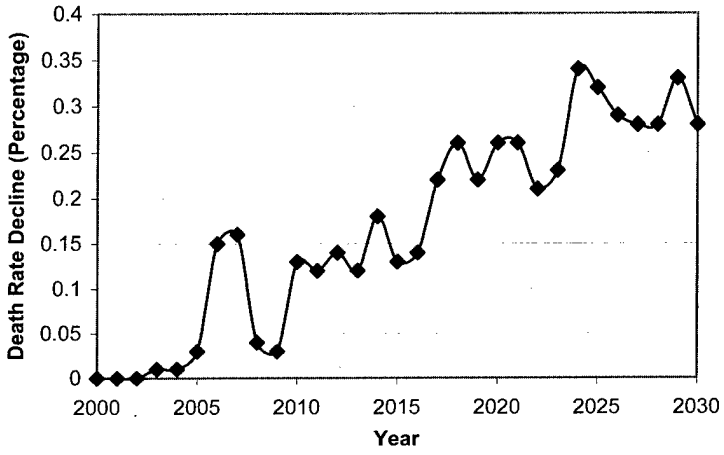


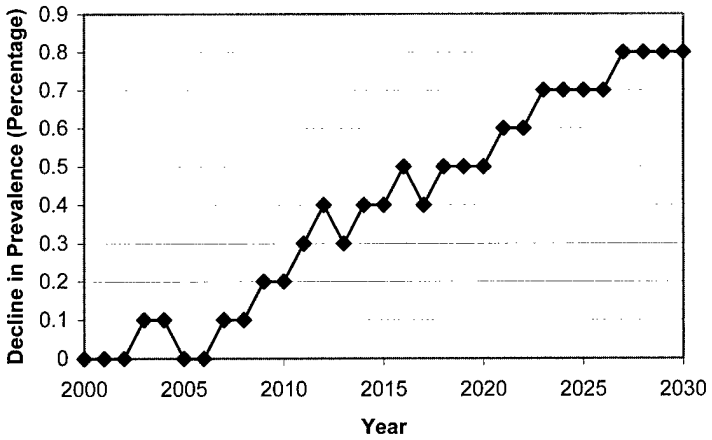
Table 8.5 shows the effect of a reduction in smoking (Smoke) on disease prevalence. Prevalence for heart disease, Alzheimer's, diabetes, hypertension, arthritis, and ADL3+ in the Smoke scenario is higher than that in the baseline scenario. Prevalence for cancer, lung disease, and ADL1+ in the Smoke scenario is lower than that in the baseline scenario. And reduction in smoking has no significant effect on stroke and nursing home residence. Figure 8.33 shows the comparison between the baseline and Smoke scenarios for lung disease prevalence. In 2030, the prevalence for lung disease in the Smoke scenario is 0.8 percentage points lower than that in the baseline scenario, an 8 percent reduction.

The changes in disease prevalence are the results of the interaction between reduction in smoking and decrease in death rate. A reduction in smoking tends to reduce the disease prevalence, whereas decreases in death rate increase disease prevalence.

Table 8.5. Disease Prevalence in 2030, Smoking Scenario

Disease	Disease Prevalence for Base in 2030 (%)	Disease Prevalence for Smoke in 2030 (%)
Cancer	16.4	16.3
Heart	40.1	41.1
Stroke	8.5	8.5
Alzheimer's	2.0	2.1
Diabetes	18.4	18.9
Lung disease	13.1	12.3
Arthritis	68.4	69.2
Hypertension	58.8	59.8
ADL1+	48.8	47.4
ADL3+	11.9	12.2
Nursing Home	5.0	5.0

Figure 8.33. Lung Disease Prevalence Decline Under Smoke Scenario



Reduction in smoking results in lower Medicare and total expenditures, as shown in Figures 8.34 and 8.35. The total savings for Medicare from 2002 to 2030 is $434.2 billion, and the total health care savings is $347.9 billion.

Figure 8.34. Cost Savings in Medicare Expenditures Under Smoke Scenario

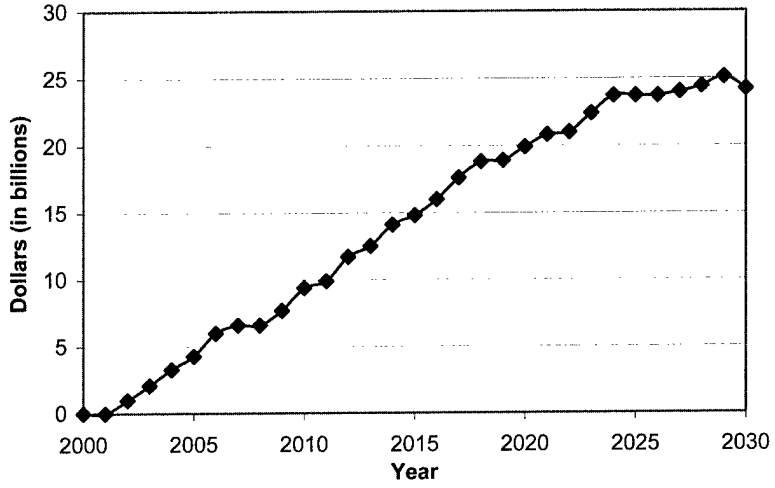
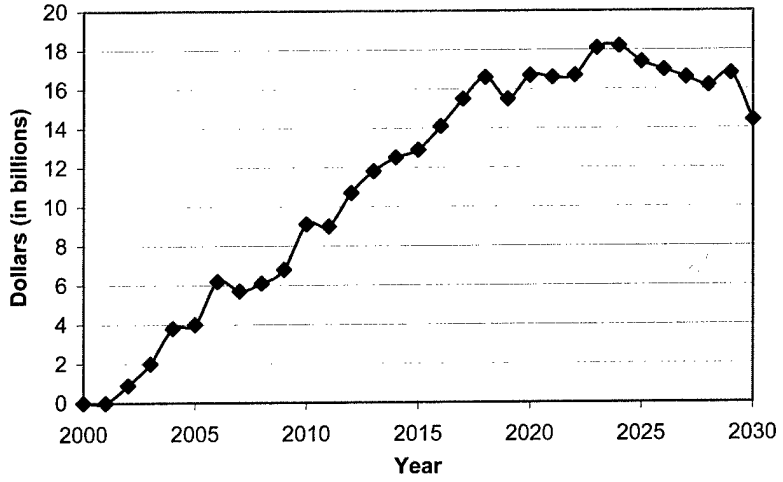


Figure 8.35. Cost Savings in Total Expenditures Under Smoke Scenario



Discussion

Just as we did in the educational attainment scenario, we designed an extreme scenario here, for exactly the same reasons. However, this choice does not mean that FEM cannot handle more realistic and complicated assumptions about future trends. In fact, FEM can easily incorporate those assumptions, as long as they are well specified. If we are willing to assume a trend in

smoking for the elderly population, FEM will be able to project its effects on health status and costs, but those effects will be somewhere between those from the baseline and the Smoke scenarios shown here.

OBESITY

Eligibility

For this simulation, obesity is defined as a body mass index greater than 30, where BMI is calculated by dividing a person's body weight in kilograms by the square of his or her height in meters. BMI is highly correlated with body fat; and a BMI greater than 30 is widely accepted as a standard of obesity for adults.

Here we consider two scenarios:
Obesity-1: Assume that no one entering Medicare after 2002 is obese (BMI > 30).
Obesity-2: Assume that no one *in* Medicare after 2002 is obese.

For those with BMI > 30, we assume their BMI = 30, which is in the omitted group in our hazard estimation.

Effect

Neither eliminating obesity for entering 65-year-olds nor eliminating obesity for all Medicare enrollees has a significant effect on the death rate, as shown in Figure 8.36.

Figure 8.36. Death Rate Decline Under Obesity Scenarios

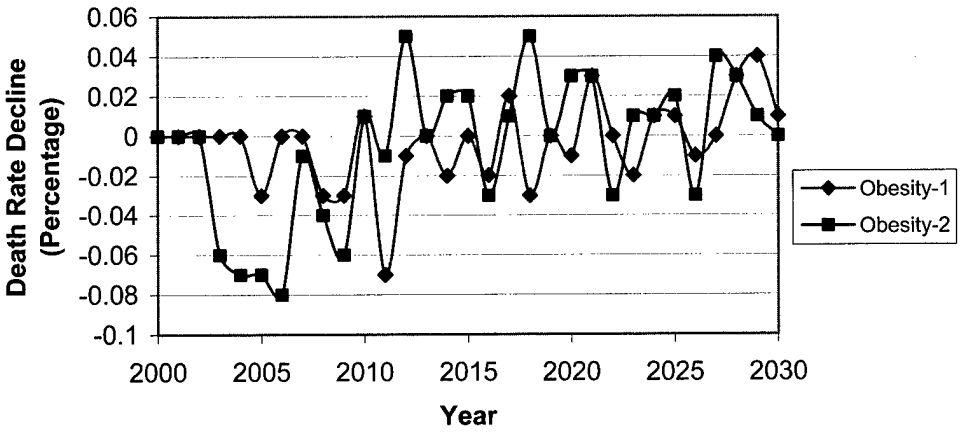


Table 8.6 shows the effect of eliminating obesity for entering individuals 65 years and over on disease prevalence. Prevalence for heart disease, diabetes, lung disease, hypertension, arthritis, ADL1+, and ADL3+ is lower in the Obesity scenarios than in the baseline scenario, and the differences gradually increase over time. Eliminating obesity has no significant effect on the prevalence of cancer, stroke, Alzheimer's, and nursing home residence.

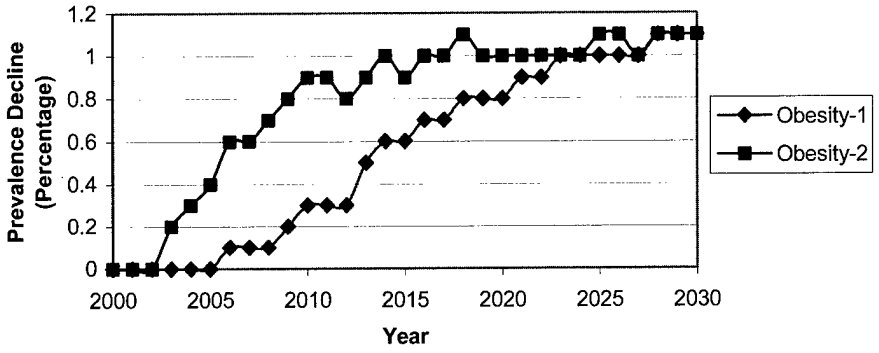
The changes in disease prevalence are the results of the lower prevalence of obesity. As shown by our hazard models, obesity strongly increases the probabilities of getting heart disease, diabetes, ADL1+, and ADL3+, and weakly increases the probability of getting arthritis and hypertension. Obesity does not enter the hazard function for cancer, Alzheimer's, and lung disease, and obesity actually decreases the probability of having a stroke and becoming a nursing home resident, but the effects are relatively small.

The difference between Obesity-1 and Obesity-2 in 2030 diminishes over time as the result of cohorts who entered before 2002 leaving the population through death. Figure 8.37 shows the comparison between baseline and the obesity scenarios for diabetes prevalence, and clearly shows the effect of Obesity-1 approaching that of Obesity-2 over time.

Table 8.6. Disease Prevalence in 2030, Obesity Scenarios

Disease	Disease Prevalence for Base in 2030 (%)	Disease Prevalence for Obesity-1 in 2030 (%)	Disease Prevalence for Obesity-2 in 2030 (%)
Cancer	16.4	16.4	16.4
Heart Disease	40.1	39.1	38.9
Stroke	8.5	8.5	8.5
Alzheimer's	2.0	2.0	2.1
Diabetes	18.4	17.3	17.3
Lung Disease	13.1	13.0	13.0
Arthritis	68.4	67.6	67.6
Hypertension	58.8	57.9	57.9
ADL1+	48.8	47.2	47.1
ADL3+	11.9	10.6	10.3
Nursing Home	5.0	5.0	5.1

Figure 8.37. Diabetes Prevalence Decline Under Obesity Scenarios



In the long run, eliminating obesity can reduce both Medicare and total expenditures, as shown in Figures 8.38 and 8.39, but the effects are very limited.

Figure 8.38. Cost Savings in Medicare Expenditures Under Obesity Scenarios

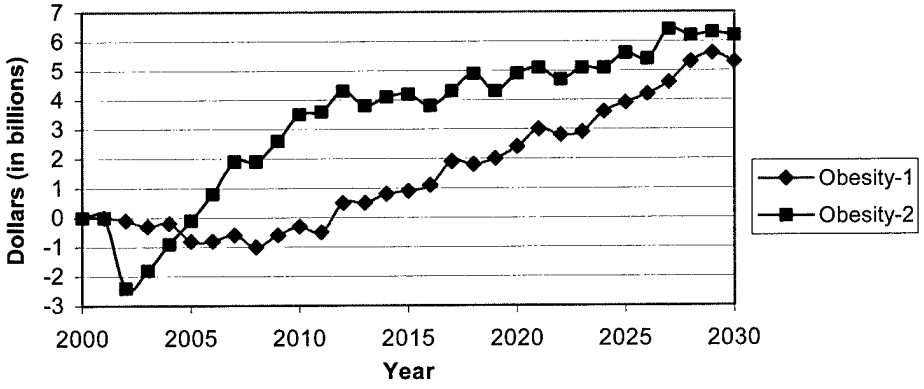
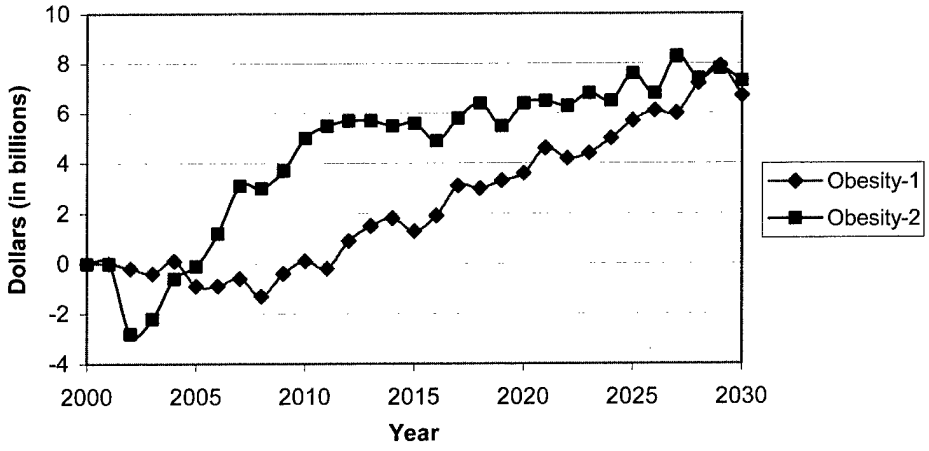


Figure 8.39. Cost Savings in Total Expenditures Under Obesity Scenarios



Discussion

Even the two extreme scenarios we designed have only minor effects on both Medicare and total expenditures. Therefore, other, more realistic assumptions will not have significant effects on them either. But those two scenarios do have significant effects on the prevalence of certain diseases, for example, diabetes.

CARDIOVASCULAR DISEASES

In this section, we describe the results of simulating the overall effect of noninvasive diagnostic imaging to improve risk stratification, MR angiography as a replacement for coronary catheterization, intraventricular cardioverter defibrillators, left ventricular assist devices, therapeutic angiogenesis, transmyocardial revascularization, control of atrial fibrillation pacemaker/defibrillators and catheter-based ablation techniques on cardiovascular disease.

Eligibility, Effect, and Costs

Table 8.7 shows eligibility, effect, and costs, and Figure 8.40 outlines the eligibility of heart disease patients for these new technologies.

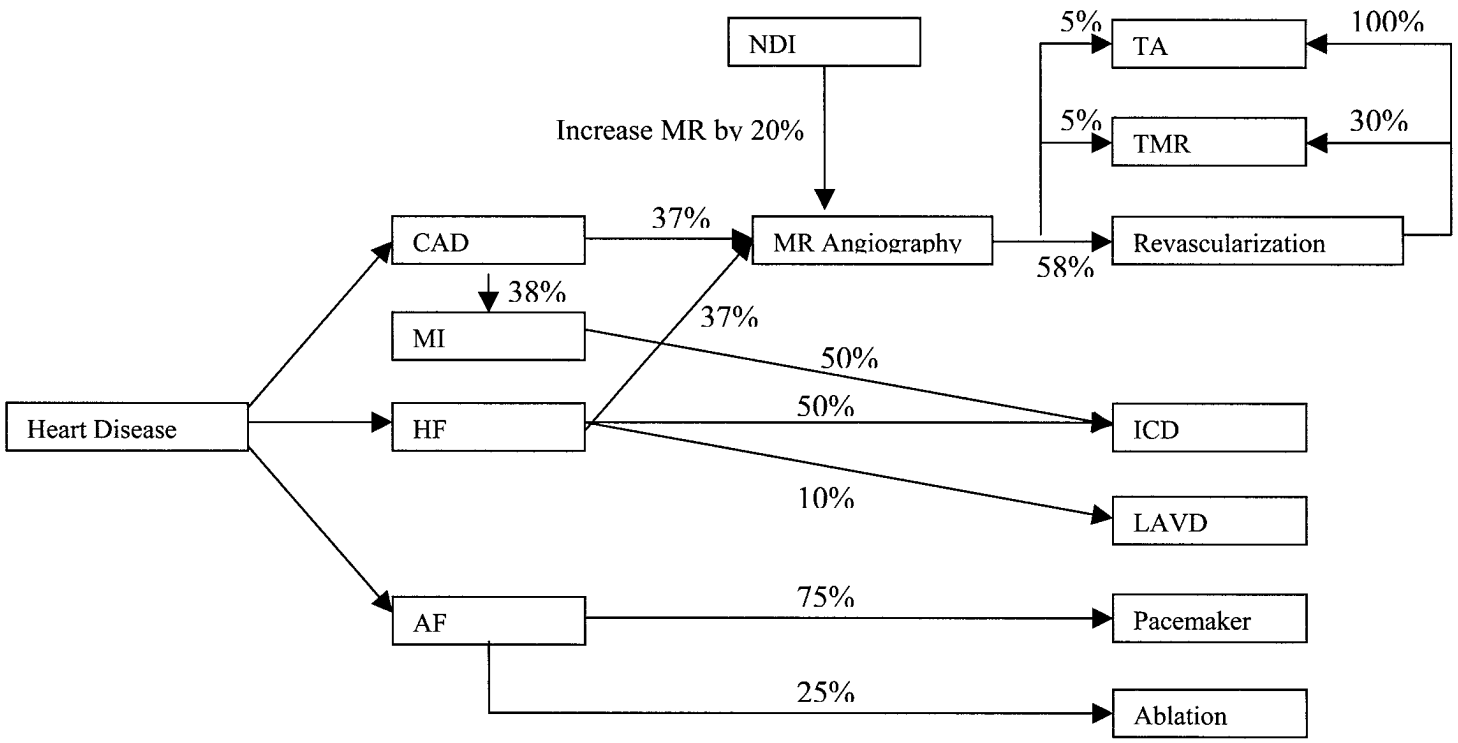
Table 8.7. Eligibility, Effect, and Costs of New Technologies for CVD

Technology	Eligibility	Effect	Cost
Noninvasive diagnostic imaging (NDI)	70-80% of the entire population is eligible for NDI.	Will better detect sub-clinical disease, and will increase use of magnetic resonance (MR) Angiography by 20%	$500 per case
MR Angiography	Potentially all patients with a diagnosis of coronary artery disease (CAD) or congestive heart failure (CHF) are eligible	Potentially all patients with a diagnosis of CAD or CHF are eligible	$1000 per case
Intraventricular cardioverter defibrillators	50% of people with HF and 50% of people with AMI are eligible	Life expectancy for people with CHF will be shifted by 6 to 10 months	$35,000 to 40,000 per case
Left ventricular assist devices (LVAD)	10% of people with HF are eligible.	General increase in ADL for persons with ADL limitations; 50% decrease in heart failure-related hospitalizations; 20% of patients will have improved 1-year mortality.	$120,000 per case.
Therapeutic angiogenesis (TA)	As a replacement for revascularization in 5% of those currently considered for revascularization; As an augmentation for revascularization in potentially 100% of people getting conventional revascularization and all patients with a diagnosis of peripheral vascular disease	Decreased number of revascularization procedures by 20-30%; Increased ADL by 10-20% due to less angina; Decreased hospitalization by 20%	$3,000 to 5000 per case
Transmyocardial revascularization (TMR)	As a replacement for 5% of those who get a cardiac catheterization but are not eligible for	Decreased number of revascularization procedures by 20-30%;	Can get directly from current CMS reimbursement schedule

	revascularization	Increased ADL by 10-20% due to less angina; Decreased hospitalization by 20%	
Pacemaker/defibrillators	All patients with ICD-9 of chronic Atrial Fibrillation (AF) or paroxysmal AF	Decreased stroke by 50% of that attributable to AF; 50% decrease in use of coumadin; 50% decrease in hospitalizations due to recurrent AF	$20,000 to 40,000
Catheter-based ablation techniques	All patients with ICD-9 of paroxysmal AF	Decreased stroke by 50% of that attributable to AF; 50% decrease in use of coumadin; 20% decrease in hospitalizations; 10% increase in need for pacemakers	$10,000 to 17,000 per case.

CAD: Coronary Artery Disease
HF: Congestive Heart Failure
AF: Atrial fibrillation
LVAD: Left ventricular assist devices
ICD: Intraventricular cardioverter defibrillators
TA: Therapeutic angiogenesis
TMR: Transmyocardial revascularization
NDI: Noninvasive diagnostic imaging
MI: Myocardial infarction

Figure 8.40. Eligibility for New CVD Treatments



The MCBS divides heart disease into three subcategories (prevalence is shown in parentheses): Myocardial infarction (14.7 percent), Coronary Heart Disease (CHD) (14.4 percent), and "other heart diseases" (27.6 percent). However, because the expert panel provided us with information about new devices to control atrial fibrillation (AF), we needed a way to identify the population with AF. The Centers for Disease Control (CDC) classification does include AF; it classifies heart diseases as follows: Coronary Artery Disease (CAD), Heart Failure (HF), and AF. CAD includes myocardial infarction and CHD. HF accounts for about 50 percent of other heart diseases. The CDC also reports that in the United States, two million people have AF and five million people have HF. In our simulation, the prevalence for all heart disease is considered to be 38.2 percent; therefore, CAD accounts for about 76 percent of all heart disease cases ([14.7 percent + 14.4 percent]/38.2 percent); HF accounts for about 36 percent of all heart disease cases ([27.6 percent/2]/38.2 percent); and AF accounts for about 14 percent of all heart disease cases (36 percent × 40 percent) (CDC, 2000). About 15 percent of strokes occur in people with AF (CDC, 2000).

We assume that 37 percent of patients with CAD or CHF receive catheterization (MR angiography) and 58 percent of patients who underwent catheterization (MR angiography) receive revascularization (Restuccia et al., 2002). The costs of catheterization and revascularization are $5,000 and $19,000, respectively (Elixhauser and Steiner, 1999).

In the simulation, MCBS beneficiaries with heart disease are randomly assigned to treatments according to the probabilities identified by the expert panel; we also assume that each patient will get each treatment no more than one time during his or her lifetime. We assume that the treatment started in year 2002. All treatments combined have no significant effects on the prevalence of any disease except stroke, as shown in Figure 8.41. Before 2002, stroke prevalence for both the baseline scenario and the Heart scenario is the same. After the treatments take effect, stroke prevalence for the Heart scenario is about 0.12 percentage points lower than that for the baseline scenario, due to the effects of pacemakers and ablation. We hypothesized that the prevalence of ADL1+ and ADL3+ would rise significantly, but it turned out that the prevalence for those conditions rose only slightly because only a small fraction of elderly were ultimately affected.

Figure 8.41. Stroke Prevalence Decline under Heart Scenario

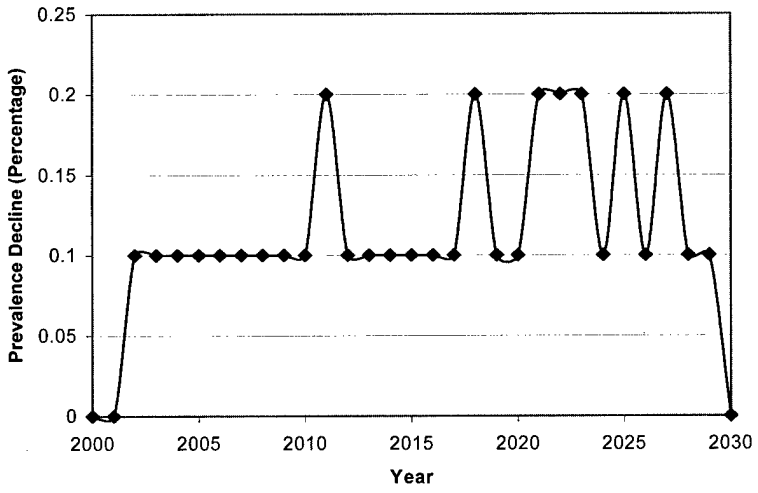
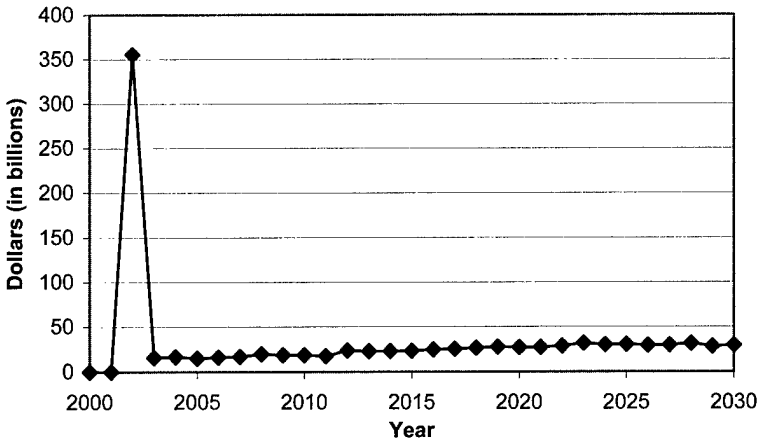


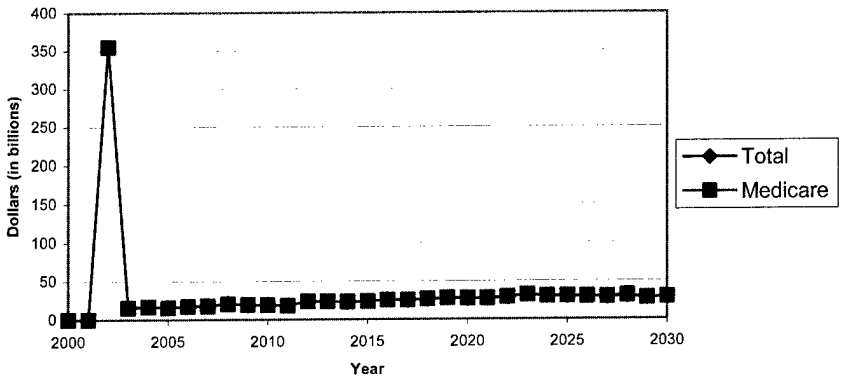
Figure 8.42 shows the total treatment costs from 2000 to 2030. There is a spike in 2002 costs, for two reasons: First, when these technologies were hypothetically introduced in 2002, patients diagnosed in the past as well as those newly diagnosed got the treatments; second, our model assumes that all patients get each treatment once during their lifetime and that the treatment occurs either when they become available or at the time the patients enter Medicare. This assumption may not hold in real-life situations; therefore, the costs would spread over a long time period.

Figure 8.42. Total Treatment Costs, Heart Scenario



The effects of treatments on Medicare and total expenditures are shown in Figure 8.43, where we show the extra costs due to treatment (Heart scenario costs minus baseline scenario costs). The results show that the treatments increase both total and Medicare expenditures, and the increase is almost the same as the treatment costs. This finding is expected, given the small changes in disease prevalence and mortality.

Figure 8.43. Total and Medicare Cost Differentials in the Base and Heart Scenarios



Discussion

Our scenario suggests that the cost of treating CVD will rise (as will overall spending), and stroke will decrease in prevalence. The difficulty in this simulation is that we have information from the expert panels on the predicted effects of these technologies only on outcomes such as hospitalization and procedure use, but we have no knowledge regarding the expected improvement in health, on which our model is built. This factor partly explains why we did not see much effect on disease prevalence.

CHAPTER 9:

USEFULNESS TO THE OFFICE OF THE ACTUARY

The Future Elderly Model is a microsimulation that projects disease, disability, and expenditures among the elderly from 2000 to 2030. It is designed to answer questions about how health status and health expenditures would change with changing disability and medical treatment.[19] This chapter considers the suitability of the model for use by the Office of the Actuary (OACT) as noted in the Final Design Report. We focus on five components of the FEM: the population projection, the expenditure projections, the econometric methodology, the what-if modeling, and the overall usefulness to OACT at the Centers for Medicare and Medicaid Services.

POPULATION PROJECTION

There are four central elements to the development of a population projection: the starting population, mortality rates, migration, and fertility rates. We will restrict our discussion to the first two elements of population projection, the starting population and mortality rates, as well as a few other methodological concerns. The projection of fertility rates is not within the scope of the FEM, as the entering Medicare cohort in 2030 (the last year of projection) was born in 1965. Likewise, although the FEM ignores immigration and emigration in the 65 and older population, in the practical use of the model, any discrepancies caused by these exclusions are likely to be relatively small and to some extent offsetting. Some Medicare beneficiaries who are eligible through alternate eligibility rules concerning supplemental security income (SSI) benefits may be missed, while any individuals 65 and older who leave the United States will be incorrectly included in the Medicare population.

Starting Population

The FEM uses Census data to determine the size of each entering cohort. The data source in the original FEM used a summary of Census population projections reported by five-year age groups. The data are then smoothed from the five-year age groups into single-age populations. This resulted in the immediate jump in the 65-and-older population in 2012, when the first baby boomers turn 65, being smoothed over several years. Table 9.1 shows rates of increase in the number of 65-year-olds. While the five-year increases are all very close, the single-year jump from 2011 to 2012 is much higher in the single-year projections.

[19] Goldman, et al., 1999.

Table 9.1. Rates of Change in Size of Entering 65-Year-Old Cohorts (percent)

	FEM	Census	SSA
2009–2014	20.1	26.3	25.7
2011–2012	3.9	36.6	14.2

It is our understanding that to address this issue, the final version of the FEM now uses single-age projections produced by the Census rather than the five-year age groups split into single years of age.

There are differences between the populations covered by the Census and Social Security Administration (SSA) population projections. As the Office of the Actuary, CMS, uses the SSA population projections for their calculations, an explanation of these differences is useful for understanding the differences between SSA and Census projections. The purpose of the SSA projections is to determine the population base eligible for the Social Security and Medicare programs. As such, SSA must include three population groups that the Census excludes: 1) those individuals missed by the Census; 2) residents of the territories and outlying areas; and 3) military residing overseas. While the Census does estimate the undercount, it is not included in their official estimates, and SSA uses the Census undercount estimate to develop its projections. As a result, SSA estimates of *current* population are generally higher than Census estimates. Projections of future populations do not necessarily follow the same pattern, as different assumptions regarding mortality, migration, and fertility are used. Table 9.2 details the population projections relevant to this discussion.

Table 9.2. Projected Population 65 or older (millions)

	FEM	Census	SSA
2005	38.614	36.370	36.624
2010	42.649	39.715	39.508
2015	48.422	45.959	45.341
2020	55.449	53.733	52.761
2025	62.552	62.641	61.383
2030	68.034	70.319	68.762

Mortality Improvement

A critical aspect of both the SSA and Census population projections is the rate of mortality improvement. The FEM uses the mortality hazard curves implied by the MCBS data from 1992 to 1998, which track very closely with Vital Statistics. By design, the FEM does not account for mortality improvement in the baseline model. As a result, although the FEM baseline population starts with a higher mortality rate than the SSA and the Census, the rate of increase slows when compared to SSA and Census in the last years of the projection.

We have compared the annual rate of mortality improvement for all individuals over age 64. The FEM baseline output implies a total mortality rate for ages 65 and over of 4.09 percent in 2001 and 4.40 percent in 2029. The ultimate assumed level of mortality improvement in 2002 Social Security's Old-Age, Survivors, and Disability Insurance (OASDI) Trustees' Report is 0.7 percent per year. The FEM output reflects only the natural increase in total mortality as the elderly population ages, whereas the SSA population clearly uses an explicit mortality improvement assumption.

The FEM approach—to allow baseline mortality to represent the status quo in the 1990s—accounts for much of the difference in sizes between the FEM-projected population and those in the Census and SSA projections. Mortality improvement in the FEM is achieved through specific changes in disease prevalence. Because the SSA and Census projections assume a rate of mortality improvement, whereas the FEM does not, there is an implicit assumption that medical advances will occur, without precisely specifying which advances these are likely to be. Thus, the FEM model is valuable for considering specific scenarios about the future using a what-if analysis, whereas the OACT model provides a more standard baseline.

The Medicare Population as a Subgroup of the Aged Population

The FEM assumes all individuals age 65 and older are covered by Medicare Parts A and B, resulting in an approximately 3 percent overstatement of the Medicare population and the resultant total costs. Included in this 3 percent are the following groups: a small number of aged individuals not enrolled in Medicare at all, a small number of aged individuals not enrolled in Part A but enrolled in part B, and a significant number of persons who are enrolled only in Part A. According to Table 4 of the 2002 Medicare Trustees' Report, there were 34.0 million elderly Federal Hospital Insurance (HI) enrollees and 32.7 million elderly Federal Supplemental Medical Insurance (SMI) enrollees in 2001. Thus, only 96.2 percent of Part A enrollees are also enrolled in Part B.

EXPENDITURE PROJECTION

Estimating Per Capita Costs

The FEM is based on four sets of regressions with dependent variables based on (1) total recorded expenditures on health care, (2) Medicare Part A benefit payments, (3) Medicare Part B benefit payments, and (4) Medicare Part A and Part B benefit payments.

The FEM model estimation of per capita expenditures excludes those with Part A only, and the (smaller) sample of those with Part B only. Thus the per capita estimates of the expenditures

for Parts A and B may differ slightly from what they would be had the entire population been used.

Observations with less than 12 months of exposure during the year were also included in the FEM regressions. The most important reason for less than a full year of exposure would be death, but other reasons could include leaving an employer plan and enrolling in Part B during a year. Without adjusting for these non-death partial year exposures, the resulting per capita estimates may differ slightly from the actual spending patterns of the population.

One actuarial technique is the calibration of model results to the actual program experience ("control totals") being modeled. In this case, that would be the counts and costs for the relevant Medicare population from program (CMS) data. This calibration process ensures that any forecast errors are in the distribution, not in the total estimate. However, whether or not such differences are important depends on how the estimates are used. If the model is used to determine only relative results—the FEM case—such differences tend to cancel themselves out, and, in any event, constitute a relatively unimportant source of potential error in interpreting the results, compared to other uncertainties necessarily involved (e.g., specifying the particular technical breakthroughs, their cost, the timing, and the relative effectiveness). In a more traditionally academic sense, calibration is defined as having the baseline model re-create the starting data. Whereas this method provides an unbiased estimate with respect to the underlying data, it does not adjust for the discrepancies between the data used and the actual program of interest. In this exercise, the FEM is calibrated to the starting MCBS data, but not to Medicare program costs.

Trending Estimates to Future Years

The FEM's baseline projection yields total expenditures for Part A, Part B, total Medicare, and the total from all sources. Per capita expenditures are also calculated for each of these four payment categories. All projected expenditures are in real terms that correspond to 1998 dollars. In order to directly compare the projections to current CMS projections, as found in the 2002 Medicare Trustees' Reports, the data must be converted to the same basis.

First, the Trustees' Report numbers have been adjusted to represent the aged population only. Next, we have discounted the TR projections using the CPI.[20] Additionally, the projections include health care costs only, whereas the CMS projections also include administrative costs. To account for this difference, we have removed 1.6 percent from the CMS projections so that we are including health care costs only. Finally, to be consistent with the data collected in the MCBS, we restrict dollars to those in the Fee-for-Service (FFS) system. We also examine what aggregate dollars would be if based on FFS per capita expenditures, but multiplied up to the total elderly Medicare population. Table 9.3 compares the FEM Medicare expenditure projections to discounted Trustees' Report numbers.

[20]This was done as follows: 2.47 percent annually between 1995 and 2000, 2.8 percent in 2001, 1.3 percent in 2002, 2.5 percent in 2003, increasing to the ultimate rate of 3.0 percent per year in 2006.

Table 9.3. Medicare Expenditures for the Elderly ($billion)

Year	FEM Projection		Discounted Trustees' Report Projection			
	Expenditures	5-Year Change (%)	FFS Per Cap * Total Pop	5-Year Change (%)	Total FFS Expenditures	5-Year Change (%)
1995	145.4		173.3		157.3	
2000	166.8	14.7	181.0	4.5	146.6	-6.8
2005	183.9	10.3	211.5	16.8	181.7	23.9
2010	202.8	10.3	254.4	20.3	217.1	19.5
2015	229.3	13.1	315.0	23.8	268.3	23.6
2020	265.0	15.6	400.2	27.0	341.6	27.3
2025	300.0	13.2	515.4	28.8	440.4	28.9
2030	330.6	10.2	655.0	27.1	559.7	27.1

Whereas the Trustees' Report value for total Medicare expenditures exceeds the FEM value for 1995, the FEM projection is growing at a much slower rate. Over the analysis period, the TR projections increase at a rate about 55 percent higher than the rate of the FEM projections. Table 9.4 compares the per capita expenditures from the FEM baseline with those for the FFS population, as based on the 2002 Trustees' Report.

Table 9.4. FFS Per Capita Medicare Expenses for the Elderly

Year	FEM Projection		Discounted Trustees' Report Projection	
	Expenditures ($)	5-Year Change (%)	Expenditures ($)	5-Year Change (%)
1995	4,330		5,353	
2000	4,649	7.4	5,447	1.8
2005	4,763	2.5	6,142	12.8
2010	4,764	0.0	6,811	10.9
2015	4,742	-0.5	7,289	7.0
2020	4,780	0.8	7,909	8.5
2025	4,800	4.2	8,726	10.3
2030	4,867	1.4	9,888	13.3

According to the CMS projections, Medicare expenditures are expected to grow at a rate far exceeding that seen in the FEM projection, even after adjusting for inflation and population growth. The only factor causing an increase in baseline projected per capita Medicare expenditures is the aging of the 65-and-older population. The growth in the Trustees' Report projections is based on a number of implicit advances in medical technology resulting in increased per capita costs. These advances are handled in a more explicit fashion by the FEM and are not considered to be part of the baseline. A baseline concept where there are no changes in the underlying morbidity and mortality cannot be reasonably expected to occur. Put differently, the FEM baseline is what would occur under the status quo of medical technology, a potentially useful concept for what-if modeling, but not necessarily for actuarial purposes. The central concept of the OACT baseline is to establish the scenario *most likely* to occur. It is these conflicting concepts of baseline that make any direct comparison between the two difficult. The modeling of a what-if scenario that mimics the assumptions in the OACT baseline would help bridge this gap.

Medicare Program Changes

In addition to modeling all costs in constant 1998 dollars, the FEM's projections are all relative to the structure of the Medicare package as it existed in the mid-1990s. The FEM's cost generation equations are based on several consecutive years of the MCBS and are adjusted for inflation but not program changes. Several changes to the Medicare program since then additionally complicate comparisons between FEM and CMS projections.

One example of such a program change is the 1997 Balanced Budget Act (BBA), which had two major implications for Medicare. The first change due to the BBA is the shift of two-thirds of Medicare-covered home health from Part A to Part B, although this ratio is dropping with the implementation of the prospective payment system. Because the FEM models the split between Part A and Part B based exclusively on pre-BBA MCBS data, this split does not reflect Medicare's current expenditure pattern. In the baseline projection, Part A accounts for 63 percent of the Part A and Part B total in 1995.[21] This proportion stays relatively constant over the projection horizon. However, because of the BBA, the percentage of the total that can be attributed to Part A has fallen dramatically since 1995. The 2002 Trustees' Report shows that Part A constituted 63 percent of the total in 1995 and 58 percent in 2000. By 2011, Part A is expected to constitute only 56 percent of total Medicare expenditures. Rather than splitting expenditures by whether they are covered by Part A or Part B, a more useful split to OACT might be either by individual type of service or by hospital versus non-hospital. Although this type of split would be the optimal situation in a model built specifically for OACT, this methodology was not pursued in the development of the FEM, based on recommendations by a panel of social science experts.

[21] As RAND has modeled Part A and Part B independently of total Medicare, this discussion will be in terms of the calculated sum of Part A and Part B.

A second change that occurred as a result of the BBA was the change in the methodology for calculating Medicare + Choice (M+C) payment rates. Prior to 1997, M+C payment rates were calculated as 95 percent of the average FFS costs in a particular county. Pursuant to the BBA, these calculations are now influenced by a number of floors, caps, and minimum annual increases. Because payment rates are no longer directly tied to fee-for-service expenditures, M+C capitation payments will constitute a different proportion of total Medicare expenditures. Over this same period, managed care enrollment has increased considerably. In December 1995, 3.8 million Medicare beneficiaries were enrolled in managed care. M+C enrollment peaked at 6.3 million in 1999 and was 5.0 million as of December 2001. This enrollment shift has increased the overall prevalence of care management in the Medicare program, and fixing the M+C enrollment at these earlier levels may result in different projections.

ECONOMETRIC METHODOLOGY

The FEM model transitions into various health statuses using a proportional hazards model. The particular states are mortality, cancer, cardiovascular disease, neurological disorders, diabetes, hypertension, and facility residence. Using data from the MCBS, regression equations calculate transition probabilities for each of the individuals in their microfile. The independent variables for each of these transitions vary and include such demographic characteristics as age, sex, race, and education. The transition probabilities also depend on the presence of other medical conditions including diabetes, cancer, heart disease, Alzheimer's disease, lung disease, osteoarthritis, high blood pressure, activities of daily living, smoking history, and body mass index. The coefficients used in these hazard functions appear to be reasonable and produce effects that are consistent with clinical knowledge—e.g., the effects of hypertension on heart disease are similar to what is found in clinical trials of beta-blockers.

WHAT-IF SCENARIOS

Examples of the what-if simulations are contained in Chapter 8. One what-if simulation shows the effect of completely eliminating hypertension. In this scenario, when the prevalence of hypertension drops to zero, the risk for heart disease falls considerably. The risk of stroke also appears to decrease somewhat, as hypertension is an important predictor for stroke in the hazard functions. The prevalence of diabetes is higher with the elimination of hypertension because these other health conditions are not predictors for diabetes. Medicare costs are much lower in the absence of hypertension. Although mortality rates are lower and Medicare beneficiaries will incur costs over a longer time horizon, the large cost savings associated with the decrease in hypertension-related hazards such as heart disease and stroke more than offset the cost of the increased life span. The decrease in Medicare costs is an instant one, being fully realized in the first year that hypertension is eliminated. After this point, costs increase at the same slope as in the baseline model. This would suggest that most of the savings are generated from individuals who would have otherwise developed heart disease and incurred significant costs but would likely have recovered and ultimately died from another hazard.

Two other simulations, which deal with obesity and diabetes, show similar reasonable results. It should also be noted that the "complete cure" scenarios illustrated in the FEM are not meant to be realistic. Rather, they are used to visibly demonstrate the mechanics of the model. The FEM has modeled more marginal changes with less dramatic but equally reasonable results.

SUMMARY

The FEM is an innovative tool and produces interesting results that will be useful in several policy venues. The FEM is especially useful as a tool for conducting what-if simulations that explain what might happen with explicit changes in demographics and medical technology. In the near term, however, the potential for applying the model in the Office of the Actuary is limited. There are three primary reasons for this observation: the different concepts of baselines, methodological issues involved in the calculation of the baseline, and the concepts underlying the specification of expenditures.

As discussed above, the FEM handles changes in morbidity and mortality from a fixed historical period resulting from an à la carte selection of medical advancements. The baseline scenario answers the following question: Under the status quo, i.e., the 1990s technology, what would be the health status of and health care costs for the elderly population in the next 30 years? It assumes no technology breakthroughs during the period. Therefore, the baseline concept in the FEM is not a scenario that can be reasonably expected to occur in the future. Rather, it is simply a starting point for analysis, much as a cost-effectiveness study would use the status quo as a reference case. In contrast, the baseline projection is designed to be the scenario most likely to occur and as such includes changes in mortality and morbidity that are based on more general trends. Technological changes are implicitly embedded in it. The first concept of a baseline is not compatible with the type of analysis that is typically done by OACT, but of course would be useful for answering specific questions about the effect of different technologies on future resource use.

The population projection on which the OACT models are based is generated annually by the OACT at the SSA. Periodically, SSA produces an actuarial note detailing the methods used to build up the assumptions behind the population projection. According to the most recent such publication,[22] the assumed annual reductions in death rates are based on an analysis of historical trends in the prevalence of specific causes of death. SSA assumes, for the 65-to-84 age group, that the ultimate annual percentage reduction in death rates will be 1.2 percent for heart disease, 0.2 percent for cancer, 1.7 percent for vascular disease, and 0.6 percent for diabetes. Compounded over 30 years, these are significant reductions that rely on implicitly assumed medical advances.

For example, if OACT were asked to model the effect of intraventricular cardioverter defibrillators (one of the many scenarios the FEM is capable of modeling) on the Medicare program, simple runs of the FEM do not provide a clear answer. OACT's underlying population

[22]Social Security Administration, 1997.

is based implicitly on projections that, from 2001 to 2030, the prevalence of death from heart disease will decrease by over 40 percent.[23] This is the baseline from which OACT's analysis must begin. The extent to which this 40 percent decline in deaths from heart disease implicitly presumes partial or complete implementation of any particular intervention is not known. In contrast, the FEM baseline presumes no further implementation of intraventricular cardioverter defibrillators or any other changes in technology that would produce changes in the age-specific prevalence of heart disease. Because of this fundamental difference in baseline concepts, the FEM could not be used to make proportional estimates. However it could be used by OACT in specific cases to compare the explicit morbidity improvement from a change to that estimated in their own baseline projections.

Conceptually, these difficulties could be overcome by adopting specific scenarios in terms of the five explicitly modeled disease classes that produce reductions in death rates similar to those projected by the SSA actuaries. One or more of these scenarios could be adopted as a baseline, and what-if scenarios analyzed relative to such a baseline. However, the work required to produce a suitable "most likely" baseline would be substantial and the analytical problems to be overcome would be non-trivial.

In addition to the issues raised by the different baseline concepts, there are several other methodological features that would make the FEM more useful to OACT. These features include the previously discussed differences in the demographic projections and the calculation of Medicare costs, and the choice of dependent variables for the regressions on which the FEM differs from a traditional actuarial approach. While the social science expert panel advised against such a classification for research purposes, it would make sense for OACT applications. They project costs in service groups that are treated differentially in the definition of Medicare benefits (including patient cost sharing), provider and payment policies, and reporting. These services include inpatient hospital, outpatient hospital, physician and other practitioner, home health agency, nursing home, laboratory, and durable medical equipment (DME). Due to size and expense, it would be reasonable to combine the smaller benefit categories (e.g., medical supplies and drugs). Important categories of services that are excluded from Medicare, but likely to be included partially or entirely in a future revision, should also be modeled explicitly (e.g., non-acute nursing home stays and prescriptions).

[23]This was determined as follows: 1.012 percent annually compounded for 29 years is a 41 percent reduction.

CHAPTER 10:
CONCLUSIONS

This project served several purposes. First, it identified possible breakthroughs that could greatly affect the future health and expenditures of the elderly. Second, we developed a microsimulation model that can be used to quantify the effect of these breakthroughs and other scenarios of interest to CMS and other policymakers. The model is flexible enough to consider life extensions and the interaction of treatment with disease, and it incorporates what is known about the health of future cohorts. Several key policy issues and recommendations arise as a result of this work.

MODELING FUTURE HEALTH AND SPENDING

The FEM starts with a nationally representative sample of beneficiaries age 65 and over in the year 1998. It then predicts health conditions and functional status next year, brings in a new sample of 65-year-olds (consisting of 65-year-olds from MCBS 1992 to1998 and reweighed to match the health status trends from NHIS and the Census population projections) and finally predicts costs. This process is repeated until 2030. A discrete piece-wise linear hazard model is used to project health transitions. The hazard of dying and getting disease depends on risk factors (sex, education, race, ethnicity, education, obesity, ever having smoked), other conditions as medically warranted, functional status, and age. A similar model is used to predict functional status. The cost regressions are based on weighted least squares with dependent variables: total Medicare reimbursement and total health care reimbursement, and independent variables: health status measures, self-reported disease categories, and interactions of health measures and disease conditions.

Figures 10.1 and 10.2 show our baseline scenario—health status and disability trends defined by 1990s technology and risk factors of the elderly population in the 1990s. In the baseline scenario, we hold the health transitions and risk factors in the elderly population constant, so the variations in disease prevalence and costs come from two sources: the health status of entering 65-year-olds and the population growth. Under the baseline scenario, the Medicare expenditures are $176 billion in 2000, $192 billion in 2005, $212 billion in 2010, $240 billion in 2015, $279 billion in 2020, $321 billion in 2025, and $360 billion in 2030.

Figure 10.1: Disease prevalence?

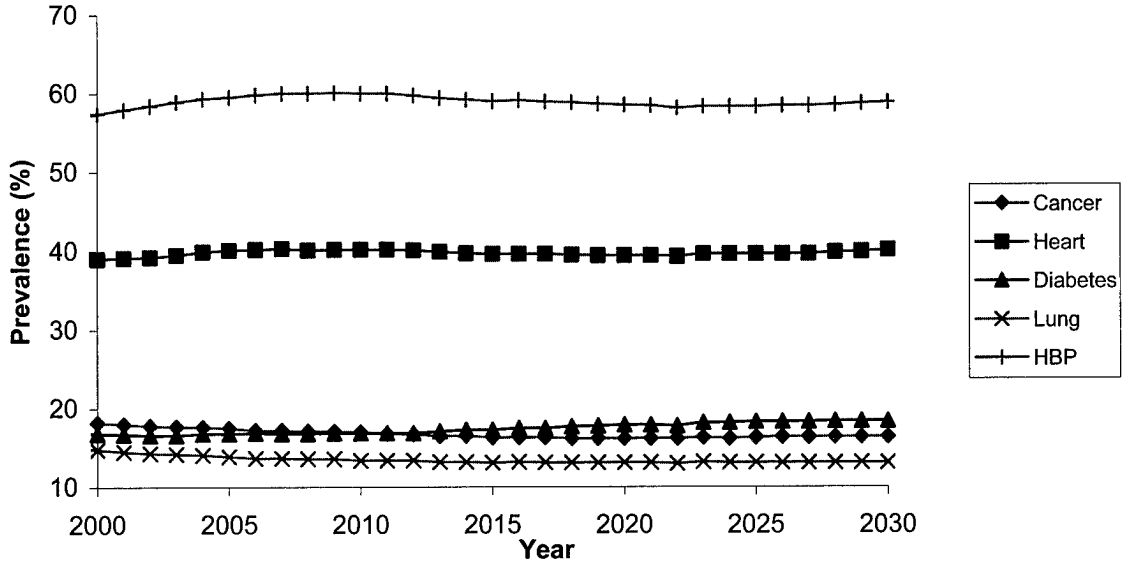
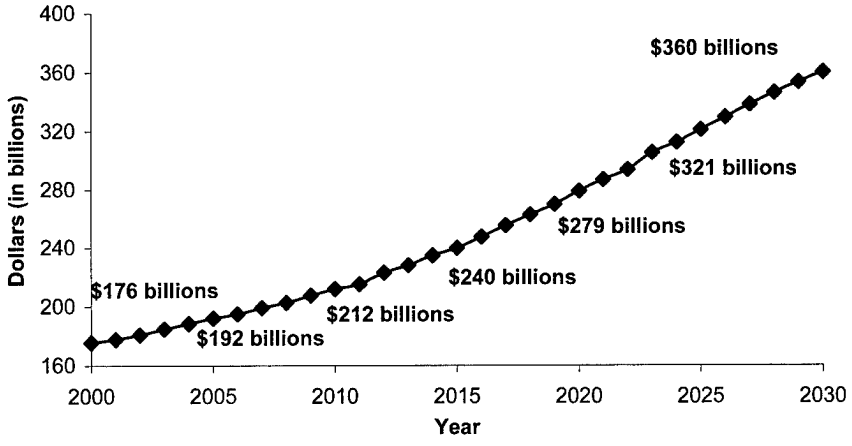


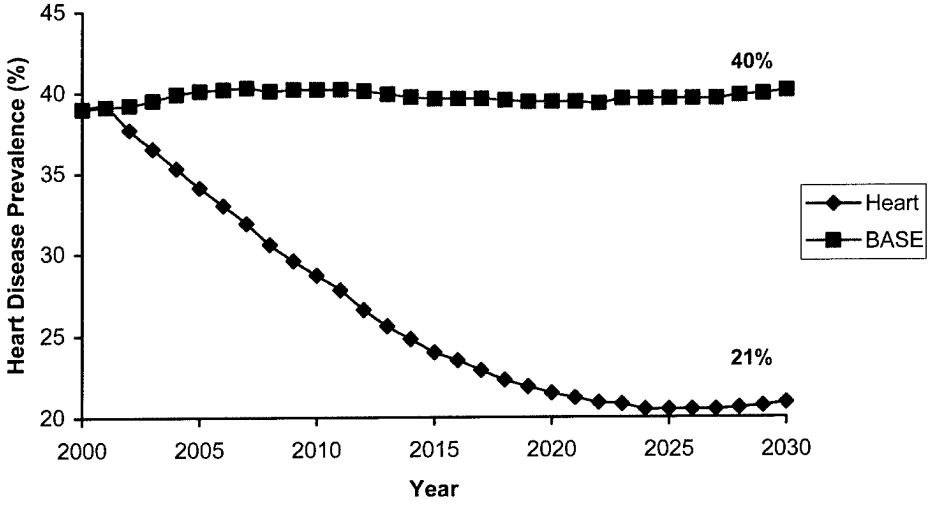
Figure 10.2. Total Medicare Costs



Breakthroughs in medical technologies or changes in risk factors in the elderly population change the health status transitions and the cost projections. Therefore, we can simulate the effects of medical breakthroughs and changes in risk factors on disease prevalence and costs by altering the health status transition parameters or risk factors among the elderly according to the assessment from the expert panel. The differences in disease prevalence and costs between the baseline scenario and the scenario with the breakthroughs will be solely due to the breakthroughs

because we hold other factors constant. Figure 10.3 shows a hypothetical example in which we eliminate heart disease among the entering 65-year-olds.

Figure 10.3. Simulating Better Heart Disease Prevention Among the Young



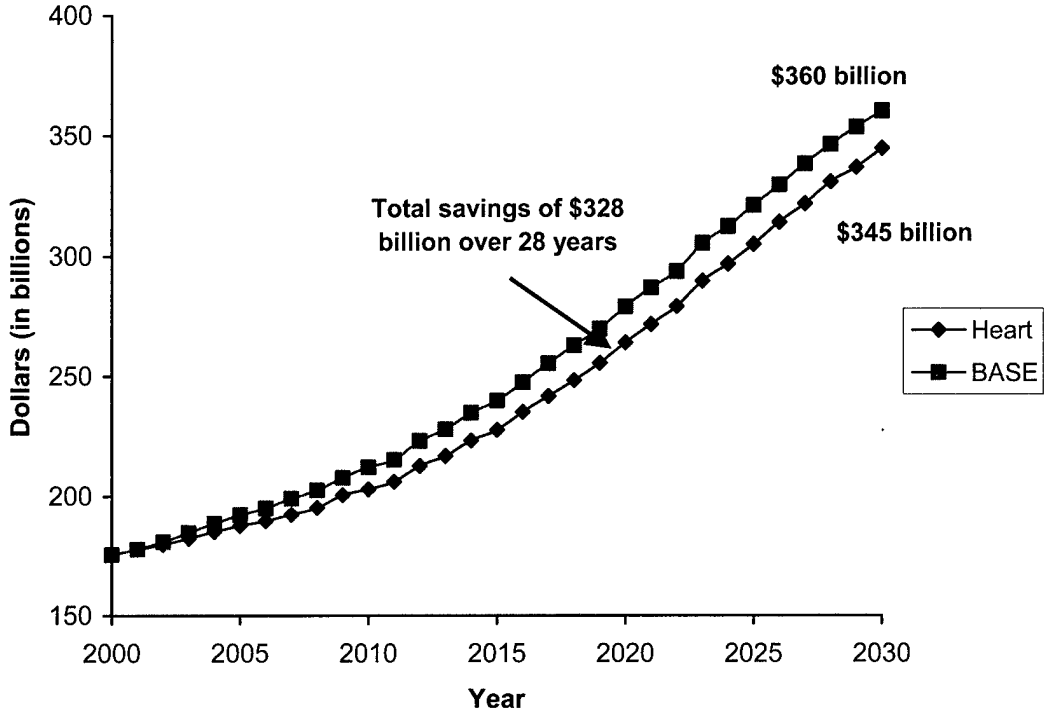
As shown in Figures 10.3 and 10.4, improving heart disease prevention among the young results in a decrease in the prevalence of heart disease and in total Medicare costs. But the mechanism is far more complicated because of the interactions among all diseases, disability, and death in the health status transitions. In this case, eliminating heart disease among the young directly reduces costs, the hazards for death, stroke, disability, and nursing home residence, but the lower death rate then increases life expectancy and exposure to the risk of other conditions, both of which result in higher costs, and so on. The FEM explicitly models these interactions and provides estimates of the net effects. Eliminating heart disease among the young would reduce heart disease prevalence by about 20 percentage points among the elderly in 2030 and save Medicare $328 billion over the next 28 years. It would also increase the prevalence of cancer, stroke, diabetes, hypertension, lung disease, and arthritis; increase the prevalence of ADL1+ and ADL3+; and have no significant effects on the prevalence of Alzheimer's disease and nursing home residence.

The simulation shows that it makes sense for Medicare to provide services to people who are younger than 65 years old and who are not yet in the Medicare program, because they will be healthier later when they do enroll in Medicare, which will reduce the total expenditures for Medicare. The simulation also estimates how much Medicare can save from treating healthier elderly. In this case, the savings would be $328 billion over 28 years after the start of preventive services in 2002. The results for scenarios that eliminate diseases other than heart disease follow the same pattern, but the exact amount of savings is scenario specific.

The simulation does not take into account the cost of preventive services, but it can be interpreted in a cost-benefit context and is useful to answer the following policy question: What is the maximum amount Medicare would be willing to pay for perfectly effective preventive services? In other words, if the cost of those preventive services is more than the savings from

treating the elderly, $328 billion in this case, Medicare would be financially worse off. Other examples can be found in Chapter 8.

Figure 10.4. Total Medicare Expenditures Under Baseline and Heart Scenarios



POLICY IMPLICATIONS

As shown in the simulations of what-if scenarios, the existing FEM can be directly used to assess the future ramifications of changes in demographic trends (e.g., better-educated future elderly and a rise in the Hispanic population) and in patient behaviors (trends in risk factors, such as smoking and obesity) because these factors are explicitly built into the FEM as covariates in the hazard models.

For changes in medical technologies in the areas of primary prevention (e.g., technologies for disease immunization) and secondary prevention (e.g., screening tests), the FEM can also be applied with only minor modifications. Examples include technologies that can eliminate heart disease among the young, a compound that extends life span, and diabetes prevention via insulin sensitization drugs.

For certain types of changes in medical technologies, moderate modifications need to be made to the FEM with detailed information on eligibility and the effect of these technologies on health status and costs. Examples include the development of telomerase inhibitors, cancer vaccines, and particular treatments for cardiovascular disease in the simulation scenarios.

For other types of changes in medical technologies and changes in the health care system, the existing FEM would need to be modified substantially. Examples include better care coordination, better medication management, and environmental improvements.

Our approach was broadly supported by our social science experts. The policy community, especially technical advisors to Medicare trustees, generally have been interested in this approach as well because of its great policy relevance. These potential breakthroughs could have important effects on future health conditions and health care expenditures, and the FEM could help CMS and other government agencies to evaluate these effects as well as the effectiveness of corresponding policies. But the FEM cannot replace the existing baseline forecasts developed by the CMS OACT and can only serve as a tool for evaluating specific trends or breakthroughs.

The work in the first part of the project also has important implications. Nationally recognized experts identified the most important potential breakthroughs in four areas: cardiovascular disease, biology of aging and cancer, neurological disease, and health services. They provided estimates about the likelihood that a breakthrough could occur, the potential effect of the breakthrough, and the potential cost implications. Their work provides important insights into the future of medicine as it affects the elderly. Several themes emerged from their deliberations:

Improved Prevention of Disease

Improved prevention of disease was the subject of breakthroughs in all three of the medically focused panels. These breakthroughs include the prevention of cardiovascular disease, the prevention of a variety of cancers with the use of selective estrogen receptor modulators, the prevention of diabetes through the use of new insulin sensitizing drugs and the prevention of Alzheimer's disease and Parkinson's disease through several different mechanisms. Nearly all of these breakthroughs have relatively low costs on a per-person basis. However, as they would need to be applied to very large populations, their cumulative costs are high. Counterbalancing these costs is the improvement in the direct cost of care related to the prevented condition and improvements in morbidity and mortality.

Better Detection or Risk Stratification of People with Early Disease

The health and expenditures of the future elderly could be dramatically affected by better detection of subclinical disease or early clinical disease. Breakthroughs in this area were identified by two panels: the cardiovascular panel and the health services panel. In both cases, the breakthroughs involve better detection of people at higher-than-average risk for poor outcomes from the chronic conditions of cardiovascular disease, depression, osteoporosis, diabetes, vision and hearing impairments, dementia, and urinary incontinence. The Human Genome Project is expected to vastly increase our ability to genotype people and determine their susceptibility to disease. Improved imaging should also increase our ability to detect subclinical disease. The concept behind this breakthrough is that better detection of subclinical disease or early clinical disease will allow for better targeting of effective therapies to try to ameliorate the progression of morbidity and mortality associated with the diseases.

Better Treatment for Patients with Established Disease

Advances in biomedical engineering are likely to be very important. Breakthroughs in this category were identified by the cardiovascular panel and included intraventricular cardioverter defibrillators, left ventricular assist devices, and improvements in atrial pacemakers and defibrillators. In general, these technologies were extraordinarily expensive on a per-person basis but would necessarily be applied only to a limited number of patients with very advanced disease.

Medical breakthroughs targeting genes or specific cells are also likely to have important consequences. Examples of these breakthroughs were identified by all three of the medical panels and include the manipulation of angiogenesis (to stimulate it in patients with poor cardiac circulation and inhibit it in patients with the neo-vascularization associated with the growth of cancer), vaccines to try to control cancer and Alzheimer's disease, and the use of small molecules targeting specific enzymes thought to be important in the development of Alzheimer's and the continued proliferation of cells that is characteristic of cancer. All of these breakthroughs tended to be of moderate cost, consistent with existing new drug therapies.

Breakthroughs in cell or organ transplantation could be much more costly. These include the use of xenotransplants for people with failing hearts and the use of stem cell transplantation for patients with Parkinson's disease or acute stroke. These breakthroughs tended to be very expensive on a per-person basis and also have a host of ethical and technological challenges facing successful implementation.

Lastly, a variety of breakthroughs identified by the health services panel involved changes in the organization and delivery of health care that could improve the receipt of effective services by persons at risk for or with established diseases. Better care management includes increasing the use of known effective interventions, better care coordination, better medication management, and improved home environment. And perhaps most important, changes in lifestyle could have the most dramatic consequences for the health and medical expenditures of the future elderly. The lifestyle issues include physical activity, obesity, diet composition, cigarette smoking, and the use of alcohol. Positive lifestyle changes were found to be substantially cost-saving.

RECOMMENDATIONS

The following recommendations address some of the limitations of the existing model.

Expand the expert panel process. Our expert panel process seems to have merit, but more assessment is needed. Ideally, this process would be made more formal and would be repeated at regular intervals. The choices made by this panel (and perhaps the best alternative) would be reviewed regularly. The alternative might include organizing panels by research areas—e.g., bioengineering or stem cells—so that experts can provide more detailed and reliable information about the breakthroughs in their areas of specialization. Key themes should be reviewed regularly. Scenarios would incorporate updated information and then make changes accordingly because of the rapid development of technologies.

Integrate the FEM into the Office of the Actuary. The FEM is an innovative tool and produces interesting results that will be useful in several policy venues. The FEM is especially useful as a tool for conducting what-if simulations that explain what might happen with explicit changes in demographics and medical technology The OACT could use the FEM in specific cases to answer questions about specific medical technologies—e.g., what would be the effects of widespread availability of implantable cardiodefibrillators or increases in education or reductions in disability. However, for it to be useful, the model needs to be kept up-to-date with recent MCBS and NHIS data.

Model complex scenarios. For technologies that may have spillovers to other specialty domains, these alternate therapeutic benefits should be considered. For example, the use of a "longevity pill" similar to caloric restriction might also lower the risk of other diseases, in addition to extending life span. More information from the expert panels about joint probabilities and treatment scenarios would be useful. We rely on the literature review and the panel assessments to precisely quantify these effects, and it needs to be done on a case-by-case basis. Past assessment of novel technologies could also assist in this effort.

Model technology diffusion. The ultimate effect of a technology depends on its timing and its price, both of which are difficult to forecast and are interrelated. For instance, our anti-obesity pill could be very expensive and have only a few users, or very inexpensive with many users. Diffusion also affects the price of services for treating cardiovascular disease and diabetes. But it is unclear how to forecast future prices in the context of our model. Ordinarily the costs of a procedure will fall over time with higher rates of adoption. In fact, there are both supply and demand effects. On the supply side, the marginal cost will fall as quantities rise, because the production technology will get more efficient. In addition, demand will increase as the price falls. From a modeling perspective, this means that scenarios that envision high rates of use need to adjust prices—even if the adjustment is ad hoc.

The price also has implications for when the breakthrough enters into clinical practice. In the FEM, we hold the transition matrix constant until a date of discovery and then apply the new transition matrix for all successive periods. It might be useful to allow uncertainty by performing the process for several different values of time to discover where the set of times is drawn from a probability distribution (Law and Kelton, 1991). However, given the speculative nature of these estimates, sensitivity analysis should be sufficient. For example, we can explore high and low estimates of effect as well as simultaneous consideration of different scenarios.

Information from the panel might also be used more formally, although the first panel had a difficult time assessing the likelihood of adoption. In many instances, their estimates ranged from 0 percent to 100 percent. In part, this variation may have represented some confusion over what these probabilities mean. Some may have interpreted the meaning to be the probability that at least one person will be treated using these methods in the future, whereas others may have interpreted it as the likelihood that any eligible person would receive this type of treatment. The latter is much closer to a prevalence rate.

Model recovery. Some of the health states in the MCBS might allow for recovery, including disability and nursing home entry. Even some of the health states such as cancer might allow for a "cure" after a five-year survival. Recovery could be modeled in several ways. Because it is

hard to predict who will recover, the easiest method is to examine the raw probabilities of people leaving states in subsequent years. This method is the opposite of the estimation underlying the FEM in modeling health transitions, which assessed the year-to-year changes in the fraction of people with a disease or functional state who do not report having it in a subsequent year, for example, the percentage of people with one or more ADL who report having none the subsequent year. One would then randomly allow the simulation sample to recover from that health state by drawing a random sample with the same percentage.

Collect additional information in the Medicare Current Beneficiary Survey. Our modeling exercise showed some of the unique benefits of the MCBS. The link between self-reported information and claims and enrollment information in Medicare is particularly useful. The MCBS suffers because it does not contain good economic data: in particular, employment, income, and wealth. Information on these economic factors would greatly improve the range of useful scenarios, because one could consider key economic trends. Furthermore, some self-reported information about disease and its treatment—e.g., whether people had angioplasty or were taking oral hypoglycemics—would also allow much better links between claims data and self-reported information.

SUMMARY

At the core of this project was the development of the future elderly model. FEM is a microsimulation model that tracks individuals over time to project health conditions, functional status, and ultimately Medicare and total health care expenditures for the elderly.

Although this approach was broadly supported by a national panel of social science experts as well as the policy community, ultimately, this project was a feasibility exercise. Could one forecast future medical breakthroughs and then simulate their effect? Our approach, to identify the key breakthroughs—using a group expert process to come up with quantifiable scenarios for future medical breakthroughs—holds great promise but must be further vetted against realizations over time, along with other mechanisms.

The real value of the FEM lies in evaluating the effects of future medical breakthroughs on health conditions and health care expenditures. The FEM can be used to predict the effects of certain key health care trends and changes in medical technology. This ability makes it useful as a global tool for answering questions about major changes in medicine. For other more specific changes in medical technologies and changes in the health care system, the model would require substantial modification. Thus, it would appear to be a useful tool for engaging in speculative what-if scenario building; for more detailed questions, more work is needed to fully assess its usefulness.

APPENDIX A:

METHODS FOR IDENTIFYING AND QUANTIFYING KEY BREAKTHROUGHS

The medical expert panels were designed to identify breakthrough technologies and provide an understanding of how specific technologies will affect the health care of the future elderly. More specifically, each panel was asked to:

1. Prioritize among the many conditions that will affect the elderly in the future and select those that affect the most people, and/or are the most costly, and/or have the biggest efffect on health status (including death)

2. For the selected conditions, identify the emerging technologies most likely to have a substantial effect on health status or cost

3. Provide for each new treatment or technology the best estimate of the potential effect on morbidity and mortality.

The medical expert panels were originally conceived as a large panel of clinicians—each with expertise in a particular area—to consider all technologies that might affect the future elderly. However, research for a RAND project assessing care for the vulnerable elderly led us to conclude that more productive discussions are possible when three or more experts represent each health domain. In consultation with CMS and a group of distinguished geriatric advisors at a meeting in San Francisco, Richard M. Allman, Christine K. Cassel, James Fries, David B. Reuben, Richard W. Besdine, and Joseph Ouslander, we modified the expert panel process to convene separate, focused panels targeted to the clinical domains of cardiovascular disease, cancer/aging, and neurological disease. Within each domain, there may be several important conditions. For example, neurological disease encompasses Alzheimer's disease, Parkinson's disease, and general cognitive impairment. In addition, the decision was made to combine cancer with aging because the two are fundamentally related at the biological level. Many normal cells have programmed senescence and cancer cells must escape this destiny to become malignant. Studies of the biology of cancer have informed the biology of aging and vice versa. A deeper understanding of the biology of aging has the potential to affect not just cancer, but all of the disorders characteristic of older age, including dementia, vascular disease, and functional decline.

The primary disadvantage to this targeted approach is that the narrow focus may ignore broader trends (e.g., changes in disease management or geriatric care) that might transcend each clinical domain. In addition, the specialists may not be as informed about the relationship between clinical and functional status as the generalists. As a result, the geriatric advisors and CMS suggested a fourth panel to address general health services issues.

To help select domains for future study, we convened a geriatric advisory panel. The panel consisted of Dr. Richard M. Allman, Dr. David B. Reuben, Dr. Christine K. Cassel, Dr. Richard Besdine, and Dr. Joseph G. Ouslander. Based on data about prevalence and costs of care, and using their own expert judgment, this group selected four domains that were most likely to have breakthroughs with major implications for Medicare costs: cardiovascular diseases; biology of

aging and cancer; neurological diseases; and changes in health services that increase the use of existing effective interventions. These choices were confirmed at a meeting of the geriatric advisory panel on November 20, 1999, in San Francisco.

SELECTION OF THE MEDICAL TECHNICAL EXPERT PANELS

We selected groups of technical experts for each of the four topic areas. We sought a broad range of expertise, including clinicians and basic scientists. We used our past experience with similar expert panels, the published literature, and the advice of local experts and CMS to select the technical experts listed below.

Cardiovascular Diseases
Dr. Melvin D. Cheitlin
Dr. Harlan Krumholz
Dr. Edward Lakatta
Dr. Eric Peterson
Dr. Michael W. Rich
Dr. Lynne W. Stevenson

Biology of Aging and Cancer
Dr. Richard N. Bergman
Dr. Judith Campisi
Dr. William Ershler
Dr. Caleb E. Finch
Dr. Richard A. Miller

Neurological Diseases
Dr. Dale E. Bredesen
Dr. George M. Martin
Dr. Howard Federoff
Dr. Jeffrey L. Cummings
Dr. Franz F. Hefti

Health Services
Dr. Richard M. Allman
Dr. Richard W. Besdine
Dr. Joseph Coughlin
Dr. David Cutler
Dr. David B. Reuben

SELECTION OF THE POTENTIAL MEDICAL BREAKTHROUGHS FOR FURTHER EVALUATION

The technical experts were surveyed for their suggestions of leading potential medical breakthroughs in each area. In making these decisions, they were asked to consider the likelihood that a breakthrough could occur, the potential effect of the breakthrough, and the potential cost implications. Responses were free text. The collated responses of the technical experts are listed in Tables A.1–A.4.

Table A.1. Suggested Breakthroughs in Cardiovascular Diseases

- More effective method for the noninvasive diagnosis of CAD and, in particular, the identification of "vulnerable" plaques
- "Cure" for hyperlipidemia, hypertension, or diabetes
- Safe and effective lusitropic agent; i.e., an agent that directly enhances diastolic function
- Tonic for vascular aging; a therapy which prevents or at least attenuates age-related vascular stiffening
- Agent which could prevent atrial fibrillation; the development of such an agent would very likely require a better understanding of the fundamental mechanisms underlying this arrhythmia
- "Successful" cardiovascular aging vs. "normal" or "usual" cardiovascular aging.
- Genetic determinants of aging, disease, and, in particular, their interactions.
- Quantitative differential patterns gene expression, including a search for additional "new" arrays of genes with altered expression.
- The levels and activity of specific growth factors and their receptors and the efficacy of growth factor signaling that underlies changes in cardiac and vascular structure.
- Molecular mechanisms that lead to disruption of vascular elastin and to vascular stiffening.
- Molecular mechanisms that lead to changes occurring within the vascular intima, as these changes strikingly resemble those that occur during early atherosclerosis.
- How the microcirculation becomes altered.
- Peripheral mechanisms that underlie reduced oxygen consumption.

Table A.1—Continued

- Specific subcellular and molecular mechanism(s) of sympathetic "overactivity," and the accompanying reduced postsynaptic responsiveness to neurotransmitters.
- New links between in vitro and in vivo senescence markers and the behavior of cardiac and vascular cells.
- How to rescue or to prevent the altered cardiac phenotype with aging, via manipulation of gene expression.
- Changes in secondary and tertiary protein structure and their effect on molecular, cellular and tissue function.
- The intensity and duration of exercise conditioning protocols required to achieve specific effects on cardiac and vascular structure and function (as well as those to lessen the risk of vascular disease).
- Specific cardiac and vascular mechanisms via which physical conditioning permits enhanced ejection capability of the heart.
- Autograft valves, with the patient's cells grown on a frame and placed under appropriate stress in vitro, then implanted.
- Heterograft hearts, probably pig hearts after genetic modification to preclude rejection.
- High-intensity medical therapy of significant, symptomatic coronary disease as an alternative to revascularization.
- Gene therapy.
- Identification of patients at genetic risk and attempting to avert that risk by either genetic or pharmaceutical therapy.
- Further advances in minimally invasive surgery.
- Genetic screening for multiple cardiovascular and central nervous system conditions is likely to become commonplace.
- Therapies for currently unrevascularizable CAD are likely to continue to proliferate.
- The widening implantation of intraventricular cardioverter defibrillators (ICDs).
- Catheter-based ablation of atrial fibrillation is clearly successful in some patients with atrial fibrillation that originates from a focus in the pulmonary veins.
- For specific drug treatment of heart failure, there is likely to be another layer of neuroendocrine modulation added to current therapies for heart failure.
- More general measures of disease management and exercise training are likely to be proven beneficial in widening populations.
- Mechanical cardiac assist devices–There is a myriad of such devices under development both for total replacement and for assistance within and around the heart.
- Xenotransplantation.

Table A.2. Suggested Breakthroughs in Biology of Aging and Cancer

- Antiangiogenesis treatment for cancer
- Vaccines to prevent cancer
- Microchip-facilitated electric synapses for neurological and paralytic disorders
- Gene therapy for age-related deficiencies and cancer
- Cloning technology to replace organs
- Artificial blood
- Improve cardiovascular functioning
- Improve control of diabetes
- Improve protection of vaccines
- Improve quality of life for cancer patients - treat cachexia and anemia
- Slow down loss of neural degenerative tissue
- Demonstrating how the evidence of prolonged life with caloric restriction could be achieved with a genetic or pharmacologic manipulation that did not involve a decrease in appetite
- Documentation of human polymorphic loci that retard age at death and retard age at onset of Alzheimer's disease, etc.
- Development of an assay for senescent cells and its use to document that such cells do not exist in aging humans or mice
- Identification of four additional single gene mutants that extend longevity in mice by 40 percent or more, and the use to compile a list of shared changes in hormone levels, cellular responses, and gene expression patterns that discriminate controls from mutants
- Selection of mouse cell lines whose cells are unusually resistant to stressful effects of heat and shock, UV light, and oxidative damage, and the use of these mice to test the idea that stress resistance will lead to extended longevity
- Construction of long lived mice by splicing genes from other, longer lived species that regulate cellular stress resistance
- Current postmenopausal hormone therapy increases the risk of breast cancer; new combinations of natural steroids and Raloxifene and other designer steroids should eventually reduce risk to zero
- Raloxifene to reduce the risk of bone fractures and heart attacks
- Genes that control lifespan in yeast, worms, flies
- Cancer, multiple forms: Use of cDNA microarrays to help individualize cancer treatment
- Cancer, multiple forms: Use of p53 and similar inhibitors to spare normal tissue during cancer treatment

Table A.2—Continued

- Cancer, multiple forms: Telomerase inhibition
- Cartilage/joint degeneration: Chondrocyte replacement: expand resident or ectopic cells (near-term), telomerize autologous cells (mid-term); generate new cells by nuclear transplantation (far-term).
- Multiple degenerative diseases: Cell replacement therapy, expand resident or ectopic cells by isolation, telomerization or nuclear transplantation to generate new cells.

Table A.3. Suggested Breakthroughs in Neurological Diseases

- Preventive therapies for many of the chronic diseases (e.g., neurodegenerative diseases).
- Genomic and /or proteomic markers predictive of specific diseases.
- Accurate imaging of virtually all tumors greater than approximately 2mm, allowing very early detection.
- Relatively effective compounds that slow aging-associated changes (e.g., relatively effective antioxidants that show activity in animal models of aging as well as human aging, where previous antioxidants have shown only very modest effects).
- Routine targeting of many drugs, including drugs to perform "bloodless surgery" (e.g., prostatectomy), target tumor vasculature, and target other drugs.
- New technologies are resulting in rational drug designs ("designer drugs"). The pace of such discoveries will accelerate and will be used, for example, for the treatment of late life depressions (e.g., targeting of specific serotonin receptors).
- The use of the relatively non-specific treatments of malignant neoplasms by chemotherapy will gradually be replaced by agents that induce terminal differentiation to non-replicative states or that enhance specific apoptosis, thus restoring the balance of cell birth versus cell death.
- There will be much greater attention to the management of the last stage of life (dying), with the introduction of behavioral, social and pharmacologic agents superior to the current approach, which mainly relies upon morphine. The revolution in rational drug design will also be generally applied to provide more efficacious management of pain.
- Vaccines or other treatments that enhance the clearance of all types of amyloid deposits (not only the beta amyloid associated with dementias of the Alzheimer type) will be developed. Similar strategies will be gradually developed for the prevention or clearance of tauopathies (a cause of frontal temporal dementias) and of synucleoses (aggregates associated with Parkinson's disease and various Lewy body disorders, including Lewy body dementias). Similar approaches will be developed for the prevention and treatment of Huntington's disease.
- A greatly improved health care management system will evolve, one that will provide long term care to all seniors without exhausting the savings of surviving spouses or children.
- A cultural, economic, political and medical paradigm shift may occur given suitable leadership and education—one that recognizes that optimum care of children will translate into healthier aging of future cohorts of seniors. This will include application of bioinformatics to diagnose special vulnerabilities requiring tailored interventions.
- Drugs that inhibit the neuropathology of Alzheimer's disease:
  The most advanced examples are inhibitors of secretases. Such drugs are likely to become available over the next 5–10 years. They will slow down the progression of the disease, perhaps even stop it completely.
- Drugs that improve memory in the elderly:
  Such drugs may be able to improve cognitive functions, memory and information processing in people with mild and advanced cognitive impairment.

Table A.3—Continued

- Drugs that inhibit the neuropathology of Parkinson's disease:
  The understanding of the disease mechanisms of Parkinson's disease lags several years behind that of Alzheimer's disease. It seems possible now that drugs will become available that slow down or even stop the progression of Parkinson's disease.
- Drugs that alleviate depression, anxiety and confusion of elderly people:
  Mechanisms of depression and anxiety are increasingly understood. It is likely that new medications will become available that do not have the negative side effects of current drugs.
- Identification of agents capable of decreasing amyloid production:
  Need to screen for early AD. Many patients held in early phases of disease.
- Neuroprotective agents found for strokes:
  Need to treat patients rapidly. Massive public education needed.
- Disease-modifying treatment for Parkinson's disease found:
  Need to screen elderly for early PD. Screening with Positron Emission Tomography (PET) possible.
- Stratification of disease risk by gene profiling:
  Application to neurodegenerative disease and stroke likely in a decade.
- Identification of environmental factors that modify inherited susceptibility to disease (Gene-environmental interactions):
  Likely to affect AD, PD, and perhaps, stroke.
- Understanding the role of the brain microvascular system as a locus for disease(s):
  New therapies predicated on manipulating or modifying the microvascular system AD and perhaps PD.
- Elucidation of mechanisms to amplify endogenous neurogenesis, direct differentiation and incorporation into existing brain:
  Neuronal repopulation and functional restoration may ameliorate neurological defects in PD and perhaps stroke and AD.
- Identification of presymptomatic molecular markers of diseases:
  Facilitate therapy with agents that disrupt disease process rather than treating symptoms.
- The application of stem cell technology, especially of mesenchymal and neural stem cells. While human pleuripotent stem cells can be obtained from fetal germ line and from the morulae of human embryos, the adult human has multipotent stem cells that can be potentially isolated, amplified and differentiated for treatments of a variety of disabilities of the host providing these stem cells, thus bypassing the problem of incompatibility. There is evidence that mesenchymal stem cells can be obtained from bone marrow. It may be possible to control the differentiation of such cells towards the myocardial lineage; such cells might be used to treat patients with congestive heart failure. These cells might also be capable of differentiating to neurons. Such cells might be used for the treatment of disorders such as Parkinson's disease.

Table A.4. Suggested Breakthroughs in Interventions in Health Services

Generic Population Interventions

- Decrease smoking
- Increase physical activity
- Increase compliance/use of processes already known to be effective (QIs)
- Change diet/ optimize nutritional status
- Reduce obesity
- Care coordination/ disease management/ community services
- Information sharing
- Markers and treatment of subclinical inflammation
- Medication management including appropriateness, error avoidance, compliance/ adherence
- Alcohol misuse
- Identification of new risk factors for some important diseases and effective therapies for same
- New rehabilitation interventions (e.g. constraint-induced therapy)
- Increased consumerism: health information, internet web sites
- Skills training for caregivers and self-management
- Environmental improvements including smart houses, smart cars, hip protectors
- Improving access to behavioral management programs
- Improved detection of underdiagnosed chronic diseases (i.e. diabetes mellitus, depression)

Population Health and Health Care Delivery

- What are hospitals going to be for?
- What will be the role of providers? (Mid-level, teams)
- What is the financing going to be, how will care be paid for?
- Medicare will be capitated
- Accountability for physical function and health-related quality of life (HRQOL)
- Drug benefit
- Global implicit assessment of effect of health service delivery change on costs and outcomes
- Integrating the payment of health and social services
- Integration of acute and long-term care payment

As a result of preliminary literature searches together with the panelists' responses, we selected the following potential breakthroughs for further review.

Cardiovascular Disease

- Therapeutic angiogenesis
- Endothelin antagonists
- Implantable cardiac assist devices
- New ways to control arrhythmias
- Noninvasive imaging of coronary artery disease
- Gene therapy for hypertension
- Xenotransplantation
- Gene therapy to cure hyperlipidemia

Cancer and the Biology of Aging

- Cancer vaccines
- Gene therapy for cancer
- Antiangiogenesis for cancer
- Xenotransplantation
- Selective estrogen receptor modulators
- The role of telomerase
- Genetic therapy for aging
- New therapies for the prevention and treatment of Alzheimer's disease

Neurological Diseases

- New therapies for the prevention and treatment of Alzheimer's disease
- New therapies for the prevention and treatment of Parkinson's disease
- Treatment of acute stroke

- New therapies for the treatment of Depression

Changes in Health Services

- Increased compliance / use of processes already known to be effective
- Care coordination / disease management / community services
- Improved detection of underdiagnosed chronic diseases (e.g., diabetes mellitus, depression)
- Medication management, including appropriateness, error avoidance, compliance / adherence
- Environmental improvements, including smart houses, smart cars, etc.
- Increased physical activity

FULL LITERATURE SEARCH

For each of the selected potential medical breakthroughs in cardiovascular disease, cancer and the biology of aging, and neurological disease, we next conducted a comprehensive literature search targeted at the breakthroughs and conditions listed above and concentrating on identifying recent relevant evidence. The details of each search are in Appendix D.

ARTICLE SELECTION

Titles and abstracts were subsequently reviewed by one of two physician investigators trained in literature searching and review, evidence-based medicine, and health services research. A sample of titles that was subjected to dual independent review revealed greater than 90 percent concordance between the two physician reviewers. We selected articles for further evaluation if they reported evidence regarding the actual or potential beneficial outcomes that could accrue from a specific intervention or if they described recent or potential future advances in a topic area or intervention. In this regard, we found that recent relevant review articles or articles announcing new advances were most useful.

PANEL MEETING

The medical technical experts met for one day to discuss the potential breakthroughs in cardiovascular diseases. We used a combination of the nominal group process to list and define potential breakthroughs for further discussion, the informal group process for the discussion of evidence and opinions regarding each topic, and formal voting to develop specific estimates for the following four areas required by the modeling team for the next phases of the project:

- The target population
- The likelihood of the breakthrough occurring in the next 10 years and the next 20 years
- Expected effect on morbidity and mortality
- Expected cost.

The nominal group process involved first presenting to the group the preliminary list of breakthroughs, then asking each panelist whether they wished to add any additional breakthroughs to the list. After this solicitation, the group discussed the relative merits of the breakthroughs and then selected the final list after this discussion.

The formal voting involved collecting from each panelist his or her estimate of the likelihood of the breakthrough occurring and the potential effect on morbidity and mortality. The process generated a range of probabilities, which will be used in the model to quantify uncertainty about the forecasts of breakthroughs. Having the range of probabilities rather than just a point estimate is an important product of the expert panel and justifies our reliance on a panel rather than on the estimates of a single expert.

MEDICAL LITERATURE REVIEW

The literature searches identified a total of 12,136 titles in cardiovascular disease, 2,029 titles in the biology of cancer and aging, and 6,751 titles in neurological diseases. Concordance between the two physician reviewers in selecting articles for further review was greater than 90 percent.

CARDIOVASCULAR DISEASE

Literature Review

This section reviews the literature relative to the potential breakthroughs identified by the panel. The breakthroughs are improved prevention of disease, NDI to improve risk stratification, xenotransplantation, therapeutic angiogenesis, implantable cardioverter defibrillator, atrial fibrillation, left ventricular assist devices, and TMR.

Improved prevention of disease. The potential efficacy of improved primary prevention was recently demonstrated by two publications. In the first (Stamler et al., 1999), data from two prospective cohorts of patients, the Multiple Risk Factor Intervention Trial (MRFIT) and the Chicago Heart Association Detection Project (CHA) were analyzed. The MRFIT study collected complete risk factor data on 342,815 men in 22 centers in 18 U.S. cities in 1975. These men were stratified into two cohorts, ages 35_39 years (72,144 men) and 40–57 years (270,671 men). The men were followed for a period of 16 years, during which there were 38,265 deaths and the cause of death was known in 98.9 percent of decedents. In the CHA study, about 25,000 men and women from 84 Chicago-area companies had baseline data collected. Three cohorts were defined: men ages 18–39 years (10,025 men); men ages 40–59 years (7,490 men); and women ages 40–59 years (6,229 women). The mean follow-up period was 22 years and the cause of death was determined for more than 99 percent of decedents. "Low risk" criteria were defined as persons with a serum cholesterol of <200mg/dL, blood pressure of <120/80, not a current smoker, no diabetes, no myocardial infarction, and no electrocardiographic abnormalities. Mortality from coronary heart disease was compared between persons in the low risk group and all others. Persons without risk factors had 77 percent to 92 percent lower mortality rates from coronary heart disease. These data directly confirm earlier estimates that the benefits of primary prevention could be a decrease of 70 percent or more in coronary heart disease mortality.

Table A.5. Mortality from Coronary Heart Disease

Cohort	Age-Adjusted Relative Risk of Low-Risk Persons Compared to All Others
Men 18-39	0.08
Men 35-39	0.14
Men 40-57	0.22
Men 40-59	0.23
Women 40-59	0.21

SOURCE: Stamler et al., 1999.

The second study assessed 84,129 women participating in the Nurses' Health Study (Stampfer, 2000). Women were 30–85 years of age at the time of enrollment (1976), and were followed for 14 years. Cardiovascular outcomes were defined as death from coronary heart disease or nonfatal myocardial infarction. Information on the cause of death was available for more than 98 percent of decedents.

Low risk status was defined as having never smoked or having stopped smoking, moderate alcohol consumption, engaging in at least one half-hour per day of vigorous or moderate activity, having a body mass index of less than 25 percent, and scoring well on a complex measure of a "healthy diet." Patients with all five low risk factors had a relative risk of coronary events of 0.17. The population attributable risk was 82 percent, meaning that 82 percent of the coronary events in their cohort may have been prevented if all women were in the low-risk group. These data support the hypothesis that adopting a healthier lifestyle could prevent the great majority of coronary disease events in women.

The currently available means of improving primary prevention is through lifestyle modification, which has not been very successful. If some as yet undiscovered "cure" became available for obesity, hypertension, diabetes, or cigarette addiction, then primary prevention could possibly be more effective.

Noninvasive diagnostic imaging to improve risk stratification. NDI has the potential to identify patients at risk for CAD or HF and to improve risk stratification. A variety of technologies have been proposed or developed to improve the status quo. The most studied technologies are electron-beam computerized tomography (CT) scanning and magnetic resonance imaging (MRI). Electron-beam CT scanning is an extremely sensitive method for detecting and quantifying the extent of calcification of the coronary arteries. Coronary artery calcium has long been identified as a marker of coronary artery disease. The presence of coronary artery calcium has been reported to be associated with a high risk for subsequent cardiac events (Arad et al., 1996). A recent study (Raggi et al., 2000) assessed the prognostic value of a calcium score as determined by electron-beam CT in 172 patients who had recently had a myocardial infarction and 632 patients who were screened and followed for a mean of 32 months. The authors reported that the rate of cardiac events in the screened cohort was highly correlated with calcium score, rising from a rate of 0.11 percent per year for subjects with a calcium score of 0 to 4.8 percent per year for subjects with a calcium score of 400 or greater.

The ability of electron-beam CT scanning to detect high-grade coronary artery occlusions and stenoses was assessed in 125 patients whose mean age was 56 (Achenbach et al., 1998). Patients also had conventional coronary angiography. Since there are four major coronary arteries, there were a total of 500 coronary arteries assessed. One hundred twenty-four arteries, or 25 percent, were considered impossible to evaluate due to technical problems. These problems included artifact due to respiration or calcification, artifacts of movement, reduced signal-to-noise rates, superposition of veins, and other causes. The accuracy of the electron-beam CT scan to detect high-grade stenoses and occlusions, compared to the gold standard of conventional coronary angiography, is listed in Table A.6.

Table A.6. Accuracy of Electron-Beam CT for the Detection of High-Grade Stenosis and Occlusions of the Coronary Arteries

Coronary Artery	Evaluation Possible (%)	Sensitivity (%)	Specificity (%)
Total	75	92	94
Left main	84	0	99
Left anterior	80	98	88
Left circumflex	66	78	88
Right	70	93	96

SOURCE: Achenbach et al., 1998.

Magnetic resonance (MR) imaging of the heart has received the most attention as the technology to replace conventional coronary angiography as a means to visualize the coronary arteries in living humans. Unlike electron-beam CT scanning, coronary MR angiography does not require iodinated contrast agents or X-ray radiation and is felt to have the potential to become a more widespread and easy to use cardiac screening tool (Duerinckx, 1999). Unlike conventional coronary angiography, MR angiography is noninvasive. However, coronary MR angiography has yet to achieve sufficient sensitivity and specificity to be considered an alternative to conventional coronary angiography. The sensitivity and specificity of reported case series are summarized in the Table A.7.

Table A.7. Sensitivity and Specificity for Coronary Lesion Detection by Coronary MR Angiography

First generation techniques	Sensitivity (%)	Specificity (%)
Manning 1993	90	92
Manning 1994	90	
Duerinckx and Urman, 1994	63 (0 to 75)	NA
Post 1994	36	
Post 1995	33	75
Pennell 1994	65	
Pennell 1994	88	
Pennell 1995	83-100	
Nitatori 1995	56	82
Mohiaddin 1996	83	98
Yoshino 1997	53-100	73-100
Post 1997	71	NA
Transition from first to second generation techniques		
Post 1994	0	
Post 1996	38	95
Second generation techniques		
Woodward 1998	80	
Müller 1996	87	97
Müller 1996	83	94
Kessler 1997	65	NA
Third generation techniques		
vanGeuns 1998	66	NA

SOURCE: References cited are from Duerinckx, 1999.

NOTE: NA = not available.

The main barrier to clinical use results from the high level of spatial and temporal resolution that is required, which is technically challenging due to the small size and tortuous nature of the vessels and their continuous physiologic motion from cardiac contraction and respiration. Another limitation results from the variable appearance of coronary lesions and the large number of image artifacts that that can be misinterpreted as coronary lesions. Despite these limitations, newer studies suggest that improvements in second and third generation coronary MR angiography techniques will soon allow adequate visualization of the coronary artery vessel wall and be used to diagnose coronary artery lesions.

Xenotransplantation. Xenotransplantation is the transplantation of organs or tissues between different species (White and Nicholson, 1999; Lambrigts, Sachs, and Cooper, 1998). The limited availability of human donor organs significantly limits allotransplantation (transplantation among the same species) to a small fraction of patients in need of transplants. This has led to increasing interest and investigation in xenotransplantation because of its potential to provide an unlimited supply of donor organs. As of 1998, there were eight reported cases of transplantation of whole organs from discordant donors (pigs, sheep, goats, rabbits) and concordant donors

(primates) in humans. In only one case was patient survival reported as greater than 72 hours. The pig has been identified as the animal most likely to provide donor organs for large-scale transplantation. Two attempts at transplanting pig hearts into humans have been reported, one occurring in 1968 and the other in 1992. In both cases, the patient survived one day or less (Lambrigts, Sachs, and Cooper, 1998). Animal models have been similarly unsuccessful. More than a dozen attempts at transplanting pig hearts into non-human primates reported survival of the recipient of a few hours to a few days.

Recently, advances in the understanding of the immune system have led to experiments with modest improvements in survival. In the past decade, 11 reports of the use of anti-pig antibody immunoadsorption (a process that removes pig antibodies from serum) in the recipient have reported survival of the recipient up to 15 days. Other attempts at reducing immunologic rejection of the transplanted heart have included the use of infused synthetic oligosaccharides or the use of human immunoglobulins to bind specific antibodies that are involved in transplant rejection, or the depletion of complement using cobra venom factor or soluble complement receptor I. Fourteen reports of attempts to transplant pig hearts into non-human primates using either method have reported survival on the order of a few days, although one study reported survival up to six weeks.

Table A.8. Results of Pig-To-Primate Heart Xenotransplantation

First Author or Surgeon/Year	Recipient	Immunologic Treatment of Recipient	Graft or Patient Survival
Ross/1968	Human	N.A.	<1 day
Religa/1992	Human	N.A.	1 day
Cooper/1988	Baboon	none	<8 hr
		Pharmacologic immunosuppression	<8 hr
Fischel/1992	Rhesus	none	2 hr
Leventhal/1993	Baboon	none	<90 min
Kawauchi/1994	Japanese	none	<14 min
	Macaques	Pharmacologic immunosuppression	30 min
Ye/1994	Baboon	Pharmacologic immunosuppression	15 min
Kaplon/1995	Baboon (newborn)	none	<82 hr
	Baboon (mature)	none	<1 hr
Kobayashi/1996	Baboon	Pharmacologic immunosuppression	40, 32, 15 min
Michler/1996	Baboon (newborn)	none	15-96 hr (mean 75 hr)
Sanfilippo/1996	Cynomolgus	none	<1 hr
		Pharmacologic immunosuppression	<1 hr
White/1996	Cynomolgus	none	45 hr (mean)
		Pharmacologic immunosuppression	0.1-6 hr
Minanov/1997	Baboon	none	<4 days
	(newborn)	Pharmacologic immunosuppression	<6 days
Kawauchi/1997	Monkey	none	<6 hr
		Pharmacologic immunosuppression	5-11 days
Itescu/1997	Baboon	Pharmacologic immunosuppression	6 days
Cooper/1988	Baboon	antibody immunoadsorption	<20 hrs (X3) 4-5 days (X4)
		antibody immunoadsorption	<24 hrs (X3) 4 days (X1)
Fischel/1991	Rhesus	antibody immunoadsorption	8 days

Ultimately, however, success will require induction of specific immunologic tolerance or the production of pig hearts without pig antigens through genetic modification of pigs. The use of a conditioning regimen that includes irradiation and drugs has achieved some level of immunologic tolerance in primates, although graft survival has still been on the order of days. Genetically engineered pigs that express human proteins have been reported. In the use of these transgenic pig organs in non-primate humans, graft survival of up to five days has been reported.

While these results indicate that much progress remains to be made before clinical trials of pig hearts in humans can be justified, these experimental studies have established that pig hearts can function satisfactorily in a foreign physiologic environment. Induction of immunologic tolerance will be necessary to provide long-term graft function and an acceptable quality of life for the recipient. Additional barriers to xenotransplantation include overcoming the need for massive and lifelong immunosuppressive therapy with its accompanying morbidity and mortality, and the potential for interspecies disease transmission from the donor to the recipient and from the recipient to the general population.

Therapeutic angiogenesis. Therapeutic angiogenesis is a technology currently undergoing human clinical trials. With this technology growth factors (naturally occurring molecules in the body that regulate growth) are used to promote the development of new blood vessels from pre-existing blood vessels (Henry, 1999; Sellke and Simons, 1999). Successful therapeutic angiogenesis has been demonstrated in animal models of coronary and peripheral ischemia using vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). Mixed results have been demonstrated in trials involving small numbers of patients with severe ischemic heart disease and peripheral vascular disease. In some cases, radiographic increases in collateral blood flow and improvements in anginal symptoms have been demonstrated. Recent Phase I studies have included a study of five male patients (ages 53–71) with severe angina unrelieved by conventional therapy who had naked plasma DNA encoding for VEGF injected directly into the ischemic myocardium via a minimally invasive procedure. All patients reported decreases in the symptoms of angina, usually beginning about three weeks after the gene therapy. This was accompanied by improvements in ischemic defects seen in myocardial imaging and improved collateral circulation in coronary angiography (Lorsodo et al., 1998). Similar results were reported in another Phase I study involving 15 male and five female patients, with seven patients being completely free of angina at six months (Symes et al., 1999). Balancing these encouraging results are those of the first randomized, placebo-controlled trial in humans. The results of this study are unpublished, but were presented at the 1999 American College of Cardiology Meeting (Mitka, 1999). In this study, 178 patients were randomized to placebo or differing doses of VEGF. Sixty-day results showed no difference in the reduction in anginal symptoms, about 60 percent, among the various groups. However, despite these "disappointing" results, investigators remain optimistic that angiogenic growth factors will prove useful in humans (Mitka, 1999). In addition to VEGF, there are numerous other angiogenic growth factors, including angiopoietin, fibroblast growth factor, insulin-like growth factor, and tumor necrosis factor. Even if VEGF does not prove to be clinically useful, investigators are encouraged by the sheer number of other growth factors available.

Growth factor proteins can be administered directly or they can be administered through gene therapy. In gene therapy, growth factors are introduced by injecting DNA or through the use of

viral vectors. Specific routes of administration include intracoronary, intramyocardial, intrapericardial, intravenous, intraarterial, and intramuscular routes. Despite some promising results, significant barriers to the therapeutic use of these growth factors remain. These include the effects on mortality, symptoms, and quality of life; risk of pathological angiogenesis; and defining the optimal growth factor, method of delivery, route of administration, dosing amount and frequency.

Implantable cardioverter defibrillator. The intraventricular cardioverter defibrillator (ICD) was first used clinically in the early 1980s (Morris et al., 1999). Controlled clinical trials have since demonstrated the value of ICDs in reducing sudden cardiac death in patients with ventricular arrhythmias (Singh, 1999). For patients with ventricular fibrillation or hemodynamically intolerable sustained ventricular tachycardia, the use of ICDs has been the standard of care for at least five years. Recent and ongoing studies have the potential to expand the use of ICDs as primary prevention in other patient populations.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) (Moss et al., 1996) reported substantial improvements in mortality at five years for patients with severely depressed left ventricular function and inducible, non-suppressible ventricular tachycardia on electrophysiologic testing who received an ICD compared with those patients managed with medical therapy alone (71 percent vs. 49 percent survival). The results of this study have expanded the use of ICDs into primary prevention of sudden death for this small group of patients.

Additional evidence for the broader therapeutic application of ICDs comes from the Multicenter Unsustained Tachycardia Trial (Schofield et al., 1999). This study randomized 704 patients with coronary artery disease, a left ventricular ejection fraction of 40 percent or less, asymptomatic unsustained ventricular tachycardia, and inducible sustained ventricular tachycardia to no antiarrhythmic therapy, antiarrhythmic drug therapy, or an ICD. All patients were followed at least two years or until the primary endpoint, cardiac arrest or death from arrhythmia, was reached. The use of an ICD, but not antiarrhythmic drug therapy, was associated with an 80 percent decrease in cardiac arrest or death from arrhythmia (Table A.9).

Table A.9. Relative Risk of Cardiac Arrest or Death from Arrhythmia with Use of ICD

Use of ICD Compared to	Relative Risk
No antiarrhythmic drug therapy	0.27
Antiarrhythmic drug therapy	0.24

SOURCE: Buxton et al., 1999.

Observational studies suggest the benefits of ICD may extend to other patient populations. A retrospective assessment of 128 patients with hypertrophic cardiomyopathy and prior cardiac arrest or sustained ventricular tachycardia who received an ICD reported appropriate activation of the defibrillator (i.e., termination of a life-threatening ventricular arrhythmia) in 23 percent of patients (Maron et al., 2000).

Two ongoing randomized trials, MADIT-II and the Sudden Cardiac Death in Heart Failure Trial (SCD-Heft) are currently testing the utility of ICD in decreasing mortality for patients with mild-to-moderate HF and no further risk stratification (Klein et al., 1999). MADIT-II is enrolling patients with at least one myocardial infarction and a left ventricular ejection fraction of 30 percent or less. Patients will be followed for 30 months. The SCD-Heft is enrolling patients with symptomatic HF and a left ventricular ejection fraction of less than 36 percent. Patients are being randomized to receive either an ICD or amiodarone (a potent anti-arrhythmic drug) or no additional therapy over standard medical management. If these clinical trials demonstrate benefits for the groups treated with ICD, the population eligible to receive ICD will enlarge substantially.

Over the past 20 years, ICD technology has progressed rapidly. Technological improvements have led to increased memory for data storage, increased device longevity, improved rhythm discrimination, and size reduction. The recent evolution of the dual-chamber ICD system has added the capability of atrial tachyarrhythmia management as a therapeutic option (Morris et al., 1999). Over the next ten years, continued improvements in ICD technology will result in continued size reduction, increased longevity, improved diagnostic capabilities, more comprehensive and specific arrhythmia therapy, easier implantation, and improved ease-of-use. ICDs have the potential to become the cardiac arrhythmia management systems of the future.

Atrial fibrillation. The next breakthrough was in the control of atrial fibrillation (AF) and included two areas: new generations of pacemakers/defibrillators and catheter-based ablation techniques. Implantable atrial pacemakers/defibrillators are still in the developmental stage and are likely to follow a course similar to that of ICDs for ventricular arrhythmias (Morris et al., 1999). Because atrial arrhythmias are not usually immediately life threatening, therapeutic endpoints will be directed towards decreasing symptoms and improving quality of life, as opposed to prevention of sudden cardiac death as in ICDs for ventricular arrhythmias. In some cases, atrial systems will occur alone, while in other cases they will be combined with ventricular systems in dual-chamber ICD systems. One concern with atrial implantable defibrillator devices is the possibility of inducing life-threatening ventricular arrhythmias with an improperly synchronized shock (Guerra and Lesh, 1999). Another concern is that patients are usually conscious when atrial fibrillation occurs and may therefore experience significant pain and discomfort with each shock. Further work will be required to develop "minimum energy" shocks, where the timing and intensity of therapy can be actively controlled by the patient.

Efforts to develop curative, nonpharmacologic treatments for atrial fibrillation have led to catheter-based ablative techniques aimed at abolishing the initiation or maintenance of atrial fibrillation to restore sinus rhythm (Guerra and Lesh, 1999). These catheter-based procedures were developed as less invasive derivatives of the Corridor and Maze surgical procedures, which require an open thoracotomy. In the catheter-based Maze procedure, radiofrequency energy is applied through a deflectable ablation catheter and used to make long linear atrial incisions as the catheter is "dragged" across the endocardium. Recent studies have demonstrated success rates of 74 percent and 90 percent in abolishing chronic atrial fibrillation, although serious complications occurred in several patients. One of the difficulties encountered is the incomplete block of electrical impulses using the linear incisions. These incomplete blocks are not effective in abolishing atrial fibrillation and may even provide an area for atrial reentry. Another problem is

that the linear radiofrequency lesions can lead to charring, local thrombus formation, and pulmonary hypertension.

Other catheter-based ablation techniques are being directed at the trigger sites for the initiation of atrial fibrillation (Guerra and Lesh, 1999). Studies have shown that atrial premature complexes frequently initiate AF and that the origin of these triggers is located predominantly in the pulmonary veins. These foci can be mapped and ablated. In one study, the long-term success of this technique in patients with paroxysmal AF was 62 percent. Limitations with this procedure include proper patient selection and having enough ectopic activity from the triggering focus at the time of the procedure to identify and localize its origin.

Left ventricular assist devices. The next breakthrough was in the use of left ventricular assist devices (LVADs). Since the inception of the artificial heart program at the National Institutes of Health in 1964, cardiac circulatory devices have been successfully used for temporary support of patients with late stage HF (New York Heart Association [NYHA] Class IV) as a bridge to transplantation (Rose et al., 1999). In select patients, use of LVADshas led to normalized hemodynamics, reversal of end-organ dysfunction, improved exercise tolerance, home discharge, return to work, and improved quality of life (Rose et al., 1999; Pennington, Oaks, and Lohmann, 1999). The evolution and success of these temporary LVADs and the limitations of the currently available treatments have led to interest in LVADs as a long-term alternative to transplantation.

A large body of evidence exists on the use of temporary LVADs as a bridge to cardiac transplantation. Data from multiple case series on over 1,700 patients at more than 120 facilities worldwide have been accumulating and demonstrate the feasibility of LVADs for long-term therapy (El-Banayosy et al., 1999; Murali, 1999; Sun et al., 1999; Poirier, 1999). A case report exists of a patient living at home with an LVAD for more than three years. This patient had severe congestive heart failure (CHF) and received an LVAD in 1995 during a hospitalization for acute decompensation that was resistant to maximum medical therapy. After receipt of the LVAD, the patient's condition improved to NYHA Class I and he was discharged home, where he has been without evidence of serious infection or thromboembolic complications (Dohmen et al., 1999). A non-randomized study compared the quality of life of 35 patients with severe HF who had received an LVAD to 55 heart transplant candidates and 97 heart transplant recipients. The study reported significant improvements in quality of life for patients after receiving the LVAD, approximating those seen by heart transplant recipients (Dew et al., 1999).

These encouraging findings have led to the first large-scale randomized study in humans, the REMATCH Trial (Randomized Evaluation of Mechanical Assistance for the Treatment of CHF) (Rose et al., 1999).

Despite their promise, there are still many concerns regarding LVADs, including the risk of thromboembolism, device malfunction, infection, dysrhythmias, bleeding, and graft complications (Pennington, Oaks, and Lohmann, 1999; Sun et al., 1999). The economic feasibility of such an intervention is also a major concern, for it has been estimated that 60,000 persons could potentially benefit from their use (Rose et al., 1999).

Transmyocardial revascularization. TMR is a surgical treatment for angina pectoris that is refractory to current standard therapy with medications, coronary artery bypass grafting,

percutaneous transluminal coronary angioplasty, or coronary artery stents. Although these current therapies are often effective, some patients with multiple, diffuse atherosclerotic lesions are not candidates for these therapies or do not respond well to these interventions, resulting in frequent angina, limited exercise tolerance, and poor quality of life. TMR creates channels through the myocardial wall to the ventricular chamber. The mechanism of therapeutic action is unclear. Postulated mechanisms include stimulation of angiogenesis and growth of existing vessels, laser channel patency with direct transmyocardial perfusion, and denervation of the myocardium.

Early, nonrandomized clinical trials using TMR reported beneficial outcomes (Frazier et al., 1995; Cooley et al., 1996; Horvath et al., 1996; Horvath et al., 1997). Three randomized controlled trials have recently been published (Burkhoff et al., 1999; Schofield et al., 1999; Frazier, March, and Horvath, 1999). Schofield and colleagues randomized 188 patients with refractory angina due to diffuse and distal coronary artery disease and reversible ischemia on radionuclide scans to transmyocardial laser revascularization or continued medical management (Schofield et al., 1999). At 12 months, there was no difference between groups in survival. However, patients treated with TMR did experience greater reductions in anginal symptoms and had fewer cardiac-related hospitalizations. Compared with 3 percent of medically treated patients, 34 percent of TMR patients achieved a reduction of two Canadian Cardiovascular Society (CCS) score classes.

Burkhoff and colleagues randomized 182 patients with angina and CCS scores of III or IV, reversible ischemia, and a poor response to prior therapies to laser TMR or continued medical therapy (Burkhoff et al., 1999). At 12 months of follow-up, 47.8 percent of patients treated with TMR had improved to CCS score II or better, compared with 14.3 percent in the medication only group. Additionally, quality of life scores, as measured by the Seattle Angina Questionnaire, improved only in the patients receiving TMR.

Frazier and colleagues randomized 192 patients with moderate-to-severe angina and coronary disease not amenable to bypass graft surgery or percutaneous transluminal coronary angioplasty to receive TMR or medical management (Frazier, March, and Horvath, 1999). At one year, patients receiving TMR had a greater reduction in anginal symptoms than did medically managed patients (reduction of at least two CCS score classes in 72 percent vs. 43 percent) and in quality of life scores (38 percent vs. 6 percent improvement on a standard instrument, the Short Form-36). There were also fewer cardiac-related hospitalizations in the TMR-treated group, but mortality between groups did not differ.

Allen and colleagues performed a similar study among 275 patients with severe angina. In this study, 76 percent of TMR-treated patients had a reduction in angina of at least 2 CCS score classes compared with 32 percent of medically treated patients at one year of follow-up (Allen et al., 1999). As seen in previous studies, there were also benefits in reduced cardiac-related hospitalizations.

The results of these studies indicate that TMR can benefit patients with diffuse, atherosclerotic disease and severe angina that is unresponsive to standard therapy. Remaining questions include whether there is a broader range of patients who could benefit from TMR, the

duration of the response, and effects on cardiovascular endpoints such as myocardial infarction and death. Table A.10 summarizes the evidence on all the cardiovascular breakthroughs.

Table A.10. Evidence Table of Breakthroughs in Cardiovascular Diseases

Breakthrough	Status of Development	Potential Barriers
Therapeutic angiogenesis	Successful studies in animal models. Several Phase I studies in humans with severe angina have reported improvement in symptoms and an increase in coronary blood flow seen on angiography. The first large randomized clinical trial reported similar outcomes between patients given vascular endothelial growth factor and placebo at 60 days follow up (relief of angina in about 60 percent of patients in both groups).	Defining the optimal agent and method of delivery. Durability of response. The risk of pathological angiogenesis.
Left ventricular assist device	An existing technology used successfully as a bridge to transplant. Advances in technology may allow for permanent implantation. Case series data report survival up to 3 years and improved quality of life in patients with severe heart failure who have received an LVAD. A large clinical trial is underway.	Demonstration of improved outcomes over current therapeutic options Effect on quality of life Patient selection Infections Thromboembolism Right ventricular failure Device failure Economic effect
Transmyocardial revascularization	Four RCTs in humans establish that transmyocardial revascularization reduces anginal symptoms about twice as well as medical therapy and reduces cardiac-related hospitalizations by 50 percent or greater than does medical management alone in patients with severe angina and coronary artery disease not amenable to surgery or angioplasty.	Optimal methods of delivery Durability of the response
Xenotransplantation	Two attempts at transplanting a pig heart into humans reported patient survival of one day or less. No successful animal models have been reported.	Xenograft rejection (hyperacute and delayed rejection) Overcoming the need for massive and lifelong immunosuppressive therapy, with its accompanying morbidity and mortality Potential interspecies disease transmission from the donor to the recipient and from the recipient to the general populations Ethical, cultural, religious issues Economic effect

*Likelihood of occurrence means widespread use in clinical practice.

Table A.10—Continued

Breakthrough	Status of Development	Potential Barriers
Implantable cardioverter defibrillators	RCTs have established the use of ICD in patients with ventricular fibrillation or sustained ventricular tachycardia reduces mortality by about 20 percent. Ongoing clinical trials may establish the benefits of ICDs extends to patients at lower risk.	Technological challenge in optimizing miniaturization and longevity for ICD Improved algorithms to simultaneously improve sensitivity and specificity of rhythm recognition Identification of genes responsible for dysrhythmias and demonstration that gene therapy has significant beneficial effects on outcomes.
Coronary magnetic resonance angiography	Clinical studies in humans report the sensitivity of detecting coronary lesions of 33 percent-100 percent compared with conventional invasive coronary angiography.	Overcoming severe technical challenges of producing images with acceptable sensitivity and specificity compared with conventional angiography. The size of the coronary arteries and their continuous motion due to cardiac contraction and breathing make visualization at the level of spatial and temporal resolution necessarily a demanding challenge.
Control of atrial fibrillation	Existing surgical procedures to disrupt the electrical pathways necessary to maintain atrial fibrillation have been modified for use with a cardiac catheter. One case series reported a 50 percent success rate but was limited by serious complications. Development and clinical testing of atrial pacemakers/defibrillators are just beginning.	Discomfort associated with size of the shock needed to convert AF New catheter technology for achieving the long lesions needed for AF ablation Reducing the risk of complications from catheter-based ablation procedures

BIOLOGY OF AGING AND CANCER

This section reviews the literature relative to the potential breakthroughs identified by the panel. The breakthroughs are telomerase inhibitors as treatment for cancer, cancer vaccines, selective estrogen receptor modulators (SERMs), antiangiogenesis, diabetes, and aging.

Telomerase inhibitors as treatment for cancer. The ends of human chromosomes contain short repeating sequences of DNA called telomeres, which are present in all eukaryotes (Vasef, Ross, and Cohen, 1999). These terminal sequences are maintained by telomerase, an enzyme that provides a template for the synthesis of the telomeric sequences. Telomerase adds repeating telomeric sequences to the chromosome ends, which prevents the telomeres from shortening (Campisi, 1997).

Most normal cells have a finite replicative life span known as the Hayflick limit (Fossel, 1998). The process that limits their proliferation is known as cellular or replicative senescence (Campisi, 1997). In the early 1970s, investigators discovered that a portion of the telomere was not replicated during cell division, and that telomeres shortened with each division (Fossel, 1998). By 1990, data had accumulated suggesting that telomere shortening results in cellular senescence. Other studies have demonstrated that lengthening the telomere can reset gene expression, cell morphology, and the replicative life span without causing malignant transformation.

Most normal somatic cells do not express telomerase (Campisi, 1997). In contrast, telomerase is expressed by most cells that do not senesce, including certain germ cells, stem cells, and tumor cells. In immortal human tumor cell lines, the average telomere length remains stable, even after multiple cell divisions. High levels of telomerase activity have been found in more than 90 percent of human neoplasms, including prostate, breast, lung, colorectal, cervical, hepatocellular, pancreatic, gastric, and renal cancers (Vasef, Ross, and Cohen, 1999). The high frequency of expression of telomerase in tumors makes it a potentially useful marker and a target for cancer treatment. Current research is evaluating the potential of telomerase inhibitors to selectively target neoplastic cells. Researchers are also exploring the potential use of telomerase for therapeutic modification of the cellular mechanisms underlying age-related diseases such as atherosclerosis, osteoarthritis, macular degeneration, dermatologic aging, and Alzheimer's disease by preventing, postponement, or reversal of natural cellular senescence (Fossel, 1998).

There are three main challenges to the use of telomerase inhibitors as anti-cancer drugs. First, the inhibitor used must be able to knock out the entire capacity of the cell to replace its telomeres. Residual ability to replace telomeres may allow the cell to continue dividing. Furthermore, experience with other cancer-fighting drugs is that incomplete knock out leads to the rise of cells that are resistant to the drugs, through natural selection. The second challenge is avoiding systemic side effects. The long-term effects of telomerase inhibition are unknown, as there are other cells of the body in which telomerase expression is normal, such as sperm cells and stem cells. The third challenge is that this strategy will only be effective for those tumors with cells that will critically shorten their telomeres before the tumor burden kills the patient. Typically, telomerase inhibition would not arrest the growth of malignant cells for 18–20 cell divisions, which means that in a living human the tumor may multiply in size 18–20 times.

Depending upon its location, such an increase in size of the tumor could threaten vital body structures and kill the patient before the telomerase inhibitor arrests cell growth. In vivo experiments using an immortalized human cell line, a human breast carcinoma cell line, and a human renal cell carcinoma cell line have all shown that telomerase inhibition has led to permanent growth arrest of these malignant cells. There are to date no published reports of the effect of telomerase inhibitors on living humans with cancer.

Cancer vaccines. Research in cancer immunology has demonstrated the ability of the immune system to destroy cancer cells. The success of animal tumor models and human clinical vaccine trials has generated interest in immunotherapy for the treatment of cancer. Immunotherapy can be classified into several different categories, including: 1) active immunotherapy–specific stimulation of the immune system using vaccines or nonspecific stimulation using adjuvants; 2) passive immunotherapy–treatment with exogenously produced antibodies; 3) adoptive immunotherapy–transfer of lymphocytes and/or cytokines; 4) restorative–replacing deficiencies in a patient's immune response; and 5) cytomedullary–enhancing the expression of major histocompatibility complex (MHC) molecules on the surface of the tumor cells (Minev, Chavex, and Mitchell, 1999). Cancer vaccines, which are usually combined with adjuvants, represent examples of active specific immunotherapy.

Active, nonspecific immune stimulants, like Bacille Calmette-Guerin (BCG), have been used successfully to treat bladder cancer (Hwang et al., 1999). Other nonspecific agents such as interleukin-2 (IL-2) and interferon-alpha (IFN-α) have shown promising results in the treatment of melanoma and renal cell carcinoma.

Numerous studies have demonstrated a beneficial role for specific stimulation of the immune system in the control of tumor growth in human and animal models. Tables A.11 through A.13 list known manipulations of the immune system against human tumors.

Table A.11. Role of Antibody in Cancer Therapy

Monoclonal Antibody (MAb)/Vaccine	Tumor Type
MAb CO17-1A	Colorectal carcinoma
Tumor cells	Melanoma
Anti-idiotype	Melanoma
Ganglioside	Melanoma
Spent media antigen	Melanoma

SOURCE: Herlyn and Birebent,1999.

Table A.12. Role of Delayed-Type Hypersensitivity in Cancer Therapy

Vaccine	Tumor Type
Tumor cells	Renal cell carcinoma
Tumor cells	Melanoma
Tumor cells	Colon carcinoma
Spent media antigen	Melanoma

SOURCE: Herlyn and Birebent,1999.

Table A.13. Role of Cytolytic T Cells (CTL) in Cancer Therapy

Vaccine	Tumor Type
Tumor cells	Melanoma
CTL (α gp 100)	Melanoma

SOURCE: Herlyn and Birebent, 1999.

Cancer vaccines require a tumor antigen that is unique to the tumor cells and a vaccine to which the host will respond (Borden et al., 1999). Tumor-associated antigens have been identified in melanoma, breast, colorectal, ovarian, lung, pancreatic, and other tumors. Some of these antigens, which include carcinoembryonic antigen (CEA), MUC-1, prostate-specific antigen (PSA), Her-2/neu, gp72, gp75, gp100, Tyrosinase, MAGE, GAGE, BAGE, and RAGE, are currently being targeted for immunotherapy (Table A.14) (Scholm et al., 1998; Minev, Chavex, and Mitchell, 1999). Vaccines using DNA, virus, bacterial, and peptide vector delivery systems have been developed that demonstrate antitumor activity in animal model systems without any significant adverse effects (Herlyn and Birebent, 1999). A number of vaccines directed against tumor-associated antigens have either completed or are undergoing Phase I, II, and III clinical trials for the treatment of colorectal cancer, breast cancer, lung cancer, prostate cancer, lymphoma, melanoma, and renal cell cancer.

Table A.14. Potential Tumor Antigens

Tumor	Potential
Bladder	BAGE, GAGE
Breast	MUC-1, CEA, MAGE, BAGE, p53
Colon	CEA, ras, p53
Head and neck	CASP-8
Lung cancer	CEA, BAGE, ras, p53
Melanoma	gp75, gp100, MART-1, tyrosinase, trp-1, trp2, MAGE, BAGE GAGE, β-catenin, ras, MUM-1, CDK-4, ESO-1
Pancreas	CEA, MUC-1, ras, p53
Prostate	PSA, PSMA, PAP
Renal cell	RAGE
Sarcoma	GAGE

From Long et al., 1999.

Cancer vaccines that are undergoing Phase III randomized clinical trials are listed in Table A.15. Two of these studies have been published. The use of autologous colorectal cancer cells with BCG adjuvant was associated with a significant clinical response in patients with colon cancer but not rectal cancer (Hoover et al., 1993). However, in a study of patients with melanoma, a cell-vaccinia virus oncolysate vaccine has not shown a benefit at present (Wallack et al., 1998). The remaining studies are unpublished.

It is hoped that advances in our understanding of the immune system and tumor immunology will lead to successful methods to stimulate a patient's own immune system to fight the cancer.

Table A.15. Cancer Vaccines in Phase III Clinical Trials

Vaccine	Adjuvant	Tumor Type	Reference
Tumor cells	BCG	Colorectal carcinoma	(Hoover et al., 1993)
Tumor cells	Vaccinia virus	Melanoma	(Wallack et al., 1998)
GM2-KLH	QS21	Melanoma	unpublished
Tumor cells	Detox	Melanoma	unpublished
Tumor cells	BCG	Melanoma	unpublished
Tumor cells	DNP	Melanoma	unpublished
STn	Detox	Breast carcinoma	unpublished
Anti-idiotype mimicking GD3	BCG	Small-cell lung carcinoma	unpublished

SOURCE: Herlyn and Birebent,1999.

Selective estrogen receptor modulators. Estrogen is a steroid that occurs naturally in the body of both men and women, and the receptors of which are found in a variety of locations, including the sex organs and the brain (Lebovitz, 1997). Estrogen levels undergo a natural decline in women after menopause. It has long been known that some breast cancers and endometrial cancers are dependent on estrogen for their growth (Lebovitz, 1997). Similarly, it is well established that estrogen deficiency is a contributing factor to osteoporosis (Lebovitz, 1997). The effects of estrogen on cardiovascular disease and neurodegeneration are less well established. The discovery that estrogen exerts its effects through different receptors opened the door to the development of modified estrogens that could have the beneficial effects on bone resorption, the cardiovascular system, and the brain while avoiding the negative effects of promoting breast cancer and endometrial cancer. Preventing breast cancer through the use of estrogen-like compounds was also envisioned. The selective estrogen receptor modulators (SERMs), as these drugs are called, that are currently approved for clinical use or in development are listed in Table A.16.

Table A.16. Selective Estrogen Receptor Modulators

Raloxifene
Centchroman
ICI 182,780
Tamoxifen
Droloxifene
Idoxifene
Toremifene
TAT-59
CP366,156

SOURCE: From Mitlak, 1999

Tamoxifen, the first such drug approved for use in humans, has been used in the treatment of advanced breast cancers since the early 1970s. It is in widespread use in the treatment of breast cancers that are estrogen receptor positive, where its use is the standard of care. The United States National Cancer Institute's Breast Cancer Prevention Trial enrolled more than 13,000 women who were at an increased risk for breast cancer but were otherwise healthy (Fisher et al., 1998). The study was stopped early by the Safety Monitoring and Advisory Committee. The principal finding was that the risk of invasive breast cancer was reduced by 49 percent (Fisher et al., 1998). The cumulative incidence at 69 months of follow-up was 43.4 versus 22.0 breast cancer cases per 1000 women in the placebo and tamoxifen groups, respectively. All of the benefit was confined to tumors that were estrogen-receptor positive (Fisher et al., 1998). Two other smaller trials, one in the United Kingdom and one in Italy, did not find a significant effect of tamoxifen on breast cancer risk reduction (Veronesi et al., 1998; Powles et al., 1998). An additional finding of the Breast Cancer Prevention Trial was that women randomized to receive tamoxifen had a 19 percent decrease in the risk of osteoporotic fractures (Fisher et al., 1998). Adverse events in the tamoxifen group included a two-fold increase in the risk of pulmonary embolism, and increases in the risk of deep vein thrombosis and stroke (relative risk 1.60–1.75). During trials of raloxifene for prevention of osteoporosis (see below), it was reported that the breast cancer rate of women receiving raloxifene was significantly lower than the rate of women receiving placebo (Cummings et al., 1999). A new trial comparing tamoxifen and raloxifene in preventing breast cancer was recently started. This trial, the Study of Tamoxifen and Raloxifene, or STAR, will enroll 22,000 women (Osborne, 1999).

Raloxifene has been extensively studied to prevent osteoporosis. The MORE trial (Multiple Outcomes of Raloxifene Evaluation) randomized 7705 women ages 31 to 80 in 25 countries who were postmenopausal for at least two years and who had osteoporosis to either raloxifene or placebo. At 36 months of follow-up, the relative risk of new vertebral fractures was 0.5-0.7 in the raloxifene group (depending on dose). The women treated with raloxifene also had increases in bone mineral density compared to women treated with placebo. However, raloxifene-treated women also had three times the risk of venous thromboembolism compared to placebo-treated women (Ettinger et al., 1999).

These results confirmed and extended the results of an earlier randomized, placebo-controlled study of raloxifene that reported benefits for raloxifene on bone mineral density and serum lipoproteins (Delmas et al., 1997).

The effect of estrogen replacement therapy on cardiovascular disease is more complicated. Individual observational studies and meta-analyses of these studies have estimated the relative risk of coronary heart disease at between 0.55 and 0.66 when comparing users of estrogen-progestin with non-users (Roe, Chiu, and Arnaud, 2000). The Heart and Estrogen/progestin Replacement Study (HERS) recently reported that among 2763 postmenopausal women randomized to estrogen replacement or placebo there was no cardiovascular benefit of estrogen and more coronary heart disease events occurring in year one in the estrogen-treated women than in women receiving placebo (Hulley et al., 1998).

A number of lines of evidence suggest that estrogens are related to neurodegeneration. Animals studied show that there are both short- and long-term responses to estrogen in the brain, including an increase in the number of excitatory synapses and long-term potentiation, both of which are felt to be experimental paradigms for memory and cognitive ability (Schneider and Finch, 1997). In rats who have had their ovaries removed, estrogen replacement therapy enhanced learning (Schneider and Finch, 1997). The evidence of an effect of estrogen on cognitive decline in humans is conflicting. Several early case control studies found no evidence to suggest that estrogens reduce the risk of dementia. Similarly, a cohort study did not find any significant association between cognitive functioning and estrogen replacement therapy among 800 women followed up for a period of 16 to 19 years. Newer case control studies and cohort studies have suggested that prior and current estrogen replacement therapy reduces the risk for Alzheimer's disease or dementia. Tables A.17 and A.18, respectively, list the results of some case control and cohort studies of the effect of estrogen replacement therapy on the risk of Alzheimer's disease or dementia.

Table A.17. Case-Controlled Studies of Estrogen Replacement Therapy (ERT) and Risk of Alzheimer's Disease (AD)

Reference	No. of Study Participants AD Cases	Controls	ERT Utilization Risk (%)	Relative Risk[a] (95% CI)
Heyman et al.	28	56	7.5-15	2.38 (0.51-9.16)
Amaducci et al.	60	60 (hospital) +50 others	8-13	0.71 (hospital) and 1.67 (others)
Broe et al.	106	106	11[b]	0.78 (0.39-1.56)
Graves et al.	60	60	16-17	1.15 (0.50-2.64)
Henderson et al.	143	92[c]	7-18	0.33 (0.15-0.74)
Brenner et al.	107	120[d]	48-49 (any form)	All users: 1.1 (0.6-1.8)
			23-28 (oral)	Oral ERT: 0.7 (0.4-1.5)
				Current oral ERT use: 0.4 (0.2-1.1)
				Lower risk with higher frequency of use
Mortel & Meyer	93[e]	148[f]	11-20	0.53 (0,27-0.94)
van Duijn et al.	124[g]	124		0.40 (0.19-0.91)[h]
Lerner et al.	78	177		0.41 (0.12-0.69)
Paganini-Hill & Henderson	138[i]	550	54	0.69 (0.46-1.03)[k]

a. Relative risk for dementia (or AD) associated with ERT use. Values <1.0 indicate a protective effect.
b. Hormone replacement therapy.
c. Volunteers.
d. Identified using pharmacy records.
e. 65 with vascular dementia.
f. Non-population-based sample.
g. With early-onset AD.
h. Risk related to apolipoprotein E4 (apoE4) allele. Early menopause and apoE4 status tended to increase the risk in individuals with a family history of AD.
i. Diagnosis of AD stated on death certificate.
j. Controls identified from 2529 deaths among a cohort of 8877 women followed for up to 11 years a s part of a study on nutrition and cancer.
k. Risk decreased with increasing dosage, longer duration of ERT, increased bodyweight and lower age of menarche.

SOURCE: Schneider and Finch, 1997.

Most of these studies show a relative risk for the development of Alzheimer's disease of about 0.4–0.7 for persons taking estrogen replacement therapy.

Table A.18. Cohort Studies of Estrogen Replacement Therapy (ERT) and Risk of Alzheimer's Disease (AD) and Dementia

Reference	Study Details	Relative Risk (95%CI)[a]	Results and Comments
Barrett-Connor & Kritz-Silverstein	800 women aged ≥ 65y included in a heart disease risk factor study. Patients were followed up for ≤ 19y.	1.90 (1.10-4.39)[b]	49.2% used ERT at baseline and 33.5% used ERT at follow-up. Prevalence of significant cognitive impairment was 3.6% at follow-up. No association between cognitive function and ERT use was found.
Tang et al.	1124 elderly women followed up for ≤ 5y	0.40 (0.22-0.85)	Among the cohort, 13.8% used ERT; 14.9% developed AD.
Kawas et al.	514 women followed up for ≤ 16y; ERT data available for 472.	0.46 (0.21-1.00)	Among the cohort, 45% used ERT; 7.2% developed AD.

a. Relative risk for dementia (or AD) associated with ERT use. Values <1.0 indicate a protective effect.
b. Relative risk calculated from death certificate evidence of dementia.

SOURCE: Schneider and Finch, 1997.

A recent meta-analysis estimated the odds ratio of 0.71 for the development of Alzheimer's disease in women taking hormone replacement therapy compared to women not on hormone replacement therapy (Yaffe et al., 1998). Another recent systematic review identified 16 prospective placebo-controlled studies in humans that assessed the effect of estrogen on memory in women. In this review, most of the studies that used neuropsychological tests found that estrogen maintained some aspects of memory in women (Sherwin, 1999).

Two ongoing randomized controlled trials, the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) are assessing the effect of estrogen replacement therapy on cognition and other outcomes. The expectation of many is that continued advances in pharmacology will be able to identify selective estrogen receptor modulators that can produce the desired beneficial effects of reducing osteoporosis, reducing breast cancer, reducing cognitive decline, and possibly reducing heart disease without increasing the risk of endometrial cancer or breast cancer, or causing troubling side effects such as endometrial bleeding, bloating, weight gain, and breast tenderness.

Antiangiogenesis. Antiangiogenesis is a novel way to approach cancer treatment. Rather than attack the cancer cell itself, antiangiogenesis attacks the cancer cell's blood supply. As a tumor grows, it must also be supplied with blood. This expansion of the existing blood vessel network is called angiogenesis. Angiogenesis is necessary for cancer growth and metastasis. Without blood flow, tumors cannot obtain oxygen and nutrients or eliminate wastes such as carbon dioxide and lactic acid (Izquierdo, 1998). Tumors cannot grow beyond a few millimeters if they do not develop new blood vessels. Successful tumor growth requires the release of growth mediators that enhance the development of tumor vascularity from neighboring capillaries (Hortobagyi, Hung, and Buzdar, 1999). Tumor vascularity is achieved through the release of angiogenesis factors that signal capillary sprouting (Izquierdo, 1998). A number of critical steps are necessary for angiogenesis to occur, and these have been targeted by investigators. They include therapies to increase levels of angiogenic inhibitors and to block the production of angiogenic stimulators.

The first angiogenesis activator, basic fibroblast growth factor (bFGF), was identified in 1982. Other growth factors and their receptors have been identified since then, including acidic fibroblast growth factor (aFGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PGDF), and angiogenin (Izquierdo, 1998; Buolamwini, 1999).

A number of angiogenesis inhibitors have also been identified. Tumor suppressor genes appear to be responsible for the production and release of these inhibitors. Suramin and its analogs are nonspecific agents that block growth factor binding to their receptors (Buolamwini, 1999). Other agents are more selective and include inhibitors of receptor kinase activity of VEGF, bFGF, or PDGF receptors. Angiostatin, thalidomide, AGM-1470 (a synthetic analogue of fumagillin), minocycline, interferons, monoclonal antibodies, matrix metalloproteinases (MMPs), urokinase (uPA), and cell adhesion molecules have also been found to inhibit angiogenesis and are being studied. For example, urokinase receptor antagonists may be useful in patients with malignant melanoma, colon, non-small cell lung, stomach, breast, and ovarian cancers (Buolamwini, 1999; Weidle and Konig, 1998). There are numerous anti-angiogenesis agents undergoing pre-clinical and clinical studies. Some of these agents are listed in Table A.19.

Table A.19. Selected Pre-Clinical and Clinical Studies on Tumor-Vasculature-Directed Agents or Strategies

Animal Studies Agent	Animal Model	Human Studies Agent
Anti-VEGF antibody	Human tumor xenografts in nude mice	Marimastat
TNP-470/AGM-1470	Human tumor xenografts in nude mice Mouse tumors in immunocompetent mice	TNP-470/AGM-1470
Angiostatin/ LBS-I	Human tumor xenografts in nude mice Mouse tumors in immunocompetent mice	Thalidomide
Truncated tissue factor	Nude mouse model of tumor vasculature targeting	CAI
Endostatin	Mouse tumors in immunocompetent mice	IL-12
RGD-doxorubicin	Human breast carcinoma cells in nude mice	Anti-$\alpha_v\beta_3$ antibody (Vitaxin)
Contortrostatin	Human breast carcinoma cells in nude mice	SU5416
		Neovastat

SOURCE: Molema and Griffioen, 1998.

Clinical results appear promising, but more research is needed to understand how angiogenesis inducers and inhibitors interact to control angiogenesis. Gene therapy using angiogenesis inhibitors is likely to become an important therapeutic option for the treatment of tumors. Current expectations are that these inhibitors will be used as adjuvants to enhance current standard therapies such as surgery, chemotherapy, and radiation therapy.

Diabetes. Diabetes mellitus has been among the top ten causes of death in the United States for several decades, and is the leading cause of end-stage renal disease and visual loss among individuals under age 65. In 1997, diabetes was responsible for approximately 2.3 million hospital admissions, 14 million hospital days, and 70 million nursing home days. Direct medical expenditures on diabetic care have been estimated at $44 billion (Lebovitz. 1997; American Board of Family Practice, 1997; American Diabetes Association, 1998). One matched cohort analysis indicated that the annual excess expenditures for diabetic patients totaled $3,500 per person (Selby et al., 1997).

More than 10 percent of persons over age 65 have clinical diabetes, the vast majority of whom have type 2 diabetes. Type 2 diabetes mellitus is a disease of relative insulin deficiency. The chief preventive measures for the disease have been the avoidance of obesity and participation in regular physical activity. Peripheral resistance to the action of insulin may play an important role in the pathogenesis of hyperglycemia. In addition, insulin resistance often accompanies other disorders such as hypertension, coronary heart disease, and obesity. This

collection of disorders, associated with certain metabolic abnormalities, is sometimes referred to as syndrome X (Komers and Vrana, 1998).

The syndrome of impaired glucose tolerance and/or syndrome X is considered to be a precursor to type 2 diabetes with an annual risk of progression to diabetes of about 2–5 percent. Therefore, persons with impaired glucose tolerance or syndrome X represent a potential target population for intervention to try and prevent onset of type 2 diabetes mellitus. The recent discovery of the thiazolidinedione-class of medications holds the promise of being a potential agent for preventing the development of type 2 diabetes mellitus in people with impaired glucose tolerance. The thiazolidinediones are a class of drugs that is chemically and functionally unrelated to other diabetes medications, including insulin, sulfonylureas, biguanides, or alpha-gluocosidase inhibitors (Johnson et al., 1998). The primary mechanism of action of the thiazolidinediones is in enhancing the insulin effects on the hepatic, skeletal, and adipose tissue. They do so without directly stimulating secretion from the pancreatic beta cells. Animal studies report the thiazolidinediones markedly reduce plasma glucose, insulin, and triglycerides concentrations in rodents that have been genetically modified to be models of insulin-resistant diabetes. In addition, thiazolidinediones drugs have been shown to reduce hyperglycemia in experimental models of insulin resistance in Rhesus monkeys (Komers and Vrana, 1998). These drugs apparently do not induce hypoglycemia in normal subjects.

There also have been reports of beneficial effects of thiazolidinediones on lipids and blood pressure. Animal models of insulin resistance have shown that treatment with thiazolidinediones markedly reduced abnormal elevated lipids (Komers and Vrana, 1998). Similar results have been observed in human studies of the effect of thiazolidinediones in patients with diabetes (Johnson et al., 1998; Brown, 2000). While some animal studies document a blood pressure lowering effect of thiazolidinediones equivalent to that achieved with conventional antihypertensive medications, results have been inconsistent (Komers and Vrana, 1998). The first drug of this class available for use in humans was troglitazone. Numerous randomized clinical trials documented the beneficial effects of troglitazone in patients with type 2 diabetes mellitus in terms of improving glucose control and increasing insulin sensitivity. However, troglitazone was taken off the market this year due to reports of liver toxicity. Still, there are two other available agents in this class, rosiglitazone and pioglitazone, and numerous others are in the pipeline. Two studies of troglitazone in patients at elevated risk for developing diabetes mellitus documented the efficacy of the thiazolidinediones in improving insulin insensitivity, glucose control, and lipid metabolism (Nolan et al., 1994; Antonucci et al., 1997). However, there are as yet no data from humans that prolonged treatment with a thiazolidinedione can prevent the development of type 2 diabetes mellitus in persons who are at risk. There are also as yet unanswered questions about the safety of long-term use.

Compounds that extend life span and improve cognition. It is important to distinguish between the median survival and the maximum survival of humans. During the 20th century, advances in public health and medicine dramatically increased the median survival. Life expectancy has been steadily rising throughout the past century and now approaches 80 years in the United States. However, during the same period of time, the maximum survival as determined by the oldest living humans has remained relatively unchanged at between 110 and 120 years. Therefore, the public health measures or advances in medicine that have greatly

contributed to increases in median life span have not affected the maximum life span. In animal models, similar limits of life span have been established. Humans live five times longer than cats, cats live five times longer than mice, and mice live 25 times longer than fruit flies (Finch and Tanzi, 1997). There is more to the genetics of aging, however, than the sequence of DNA. Mice and bats have a 0.25 percent difference in their primary DNA sequence, yet bats live for 25 years, which is ten times longer than mice (Ershler and Longo, 1997). Therefore, regulation of gene expressions seems likely to be the source of differences in longevity between species. Whether it is a small number of genes or a large number of genes that are responsible is unknown.

There have been several in vitro and animal studies that have documented ways to prolong life. One of the best known is the effect of caloric restriction. For more than 50 years, it has been known that rodents fed a nutritionally complete diet that contains 30 percent to 40 percent fewer calories than they would normally consume given free access to food live up to 50 percent longer than other rodents eating at will (Miller, 1997). This life span extension involves a deceleration of the aging process as measured by a wide range of biochemical, genetic, and physiological markers, all of which are retarded in parallel. The largest effects are seen when caloric restriction has begun early in life, but some effect is seen even when caloric restriction is begun in middle age. Median and maximal life span are both affected. There have been many suggested hypotheses explaining this effect. Three that have been refuted are that caloric restriction works by retarding growth, or that it works by reducing the ingestion of toxic substances, or that it works by lowering the amount of energy utilization per gram of metabolizing tissue (Miller, 1997). Furthermore, the argument that some authors have made that caloric restriction merely restores the normal level of food intake that an animal would consume in the wild, as opposed to an overfed laboratory rodent is inconsistent with the observation that most calorically restricted rodents in the laboratory are infertile. Hypotheses for which there is ongoing research include the effects of caloric restriction on diminishing blood, glucose, and insulin levels; increases in the free glucocorticoid levels; the altered expression of heat shock genes; and the change in resistance to free radical mediated damage. What is unknown is whether any of these well-observed effects is in fact the primary mechanism by which caloric restriction prolongs life, or whether these are merely secondary effects of some other primary mechanism. There are at least three studies underway that are attempting to determine whether the effect of caloric restriction also prolongs life in primates. There are as yet no results, nor can any be expected soon, given that primates live for decades. Understanding how caloric restriction works could have profound implications for disease prevention and life prolongation. A method to reproduce the effects of caloric restriction using pharmacology could potentially prolong life by up to one-third and forestall the appearance of diseases associated with aging such as Alzheimer's and macular degeneration until near the end of life.

A second example of the ability to influence the aging of animals is the gene experiments modifying the life span of fruit flies and nematodes. In the nematode *Caenorhabditis elegans*, six induced mutations can extend life expectancy between 40 and 100 percent (Finch and Tanzi, 1997). The first such mutation identified was *age-1* which doubles the maximum life span. The life-extending mutations work by increasing resistance to stressors, including temperature, free radicals, and ultraviolet light. Also, the regulation of nematode life span by insulin-like signaling is compatible with the previously mentioned extension of life span in rodents by food restriction. That humans share a specific genetic mechanism associated with longevity is supported by the

recent identification of the gene responsible for the Werner Syndrome, which is a rare autosomal recessive adult-onset disease characterized by the early manifestations of aging such as hair loss, skin atrophy, premature heart disease, and various tumors. The Werner gene resembles a DNA helicase, and loss of function in this gene leads to impaired DNA replication or DNA repair, resulting in the accumulation of various DNA mutations and a rapid decrease in telomere length.

The third example of laboratory investigations to prolong life involves telomerase. As previously discussed in the section concerning telomerase and cancer, the DNA of cells has short repeating segments at the ends called telomeres, one of which is lost on each cell division. At a certain critical length, cells no longer divide and the cell undergoes a complex series of physiologic changes leading to senescence. This replicative senescence is felt by many to be an evolutionary mechanism to protect the organism from cancer (Fossel, 1998). Indeed, most cancers express the enzyme telomerase, which resets the telomere clock at each division, thereby making possible an infinite number of cell divisions. Replicative senescence then is, in the words of one author, the "double-edged sword" that both helps prevent death from cancer but causes cell and organismal aging (Campisi, 1997). There are now numerous reports that ways to effect telomerase activity can be successful, can reset the cellular clock, and permit a reset of the gene expression in a cell from a senescent state to a youthful state (Fossel, 1998; Bodnar et al., 1998; Yang, 1999). As yet, there have been no applications of this outside of cell cultures.

The discovery of a pharmacologic or gene mechanism that could reproduce the effects of caloric restriction, or affect a small number of genes responsible for aging, or promote a re-lengthening of telomeres without inducing cancer would be a major step in increasing the maximum life span. Table A.20 summarizes the evidence on all the cancer and biology of aging breakthroughs.

Table A.20. Evidence Table of Breakthroughs in Cancer and the Biology of Aging

Breakthrough	Status of Development	Potential Barriers
Telomerase Inhibitors for Cancer	Successful in vitro experiments using telomerase inhibitors to arrest growth of human cancer cells.	Identification of inhibitor molecule that can be easily targeted to cancer cells Need to knock out entire telomerase capability Avoid serious side effects Demonstration of clinical benefit in humans with cancer
Cancer Vaccines	Many successful animal models, successful anecdotes in humans, particularly with melanoma and renal cell carcinoma. One successful and one unsuccessful phase III randomized clinical trial in humans	Identification of optimal antigen and adjuvant Demonstration of clinically important benefit Possible side effects
Selective Estrogen Receptor Modulator	Successful randomized trials in humans documenting the use of SERMs to prevent breast cancer and prevent osteoporosis	Developing SERMs that produce the beneficial effects without also causing the deleterious side effects
Antiangiogenesis	Many successful animal studies. Anecdotal reports of success in humans. Phase III randomized studies in humans are ongoing	Demonstration of clinically important benefits in humans Avoiding serious side effects
Use of Thiazolidinediones to Prevent Diabetes Mellitus	Successful animal models. Successful small human studies reporting normalization of glucose metabolism in persons at high risk for diabetes.	Demonstration of clinically important benefits in humans Avoiding serious side effects (the first thiazolidinedione was withdrawn due to fatal liver toxicity)
Extended Life Span	In vitro and animal models documenting that caloric restriction, or a small number of genes, or telomerase, can result in prolonged life and/or a reversal of cellular senescence.	Demonstration of clinically important benefits in humans Avoiding serious side effects

*Likelihood of occurrence means widespread use in clinical practice.

NEUROLOGICAL DISEASES

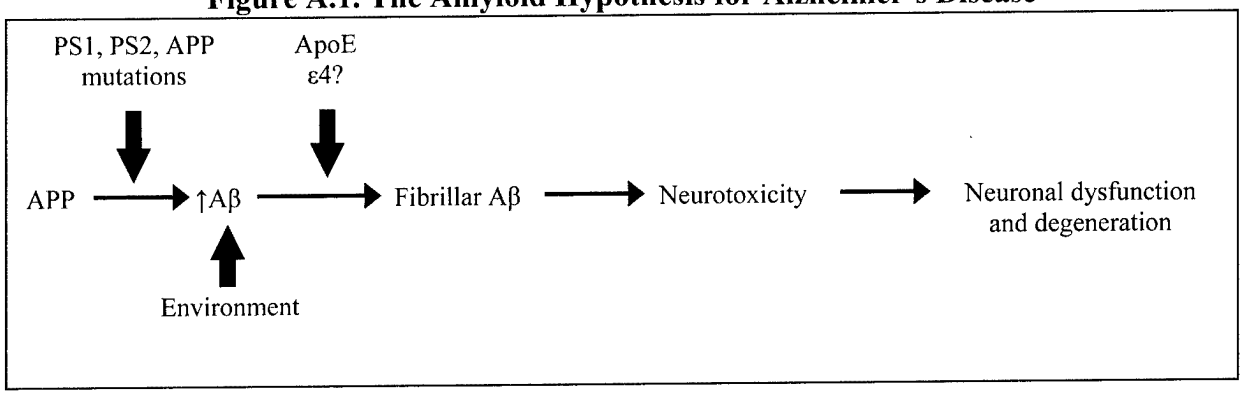
This section reviews the literature relative to the areas of potential breakthroughs identified by the panel. The areas for relevant breakthroughs are Alzheimer's disease, Parkinson's disease, prevention and treatment of acute stroke, and depression.

Alzheimer's Disease

Alzheimer's disease (AD) is the progressive loss of memory and cognitive function, and affects nearly 50 percent of people over the age of 85. It is characterized pathologically by the development of plaques of beta-amyloid (Aβ) found in the brain cells. Until the mid-1980s there was no specific therapy for AD. Since the demonstration of statistically significant, albeit modest, benefits in terms of cognition for cholinesterase inhibitors (Knapp et al., 1994; Rogers et al., 1998), a variety of pharmacotherapies are being developed. At the same time considerable work has been performed on understanding the molecular structure of amyloid and methods for decreasing the production of amyloid or actually removing it once it has appeared. These two lines of therapy are reviewed here.

Therapies based on the amyloid hypothesis. The amyloid hypothesis states that beta-amyloid deposits in the brains of patients with AD are responsible for the disease (Figure A.1). This hypothesis stems from the identification of beta-amyloid deposits in the pathologic diagnosis of AD. In this model, amyloid precursor protein (APP) is cleaved by secretases to form Aβ. Mutations of the genes responsible for APP and two other proteins, the presenilins, are known to cause rare forms of early onset Alzheimer's. Possible environmental agents may also be involved in the development of Aβ. Fibrillar Aβ then causes the neurotoxicity and neuronal dysfunction characteristic of Alzheimer's disease.

Figure A.1. The Amyloid Hypothesis for Alzheimer's Disease



SOURCE: St. George-Hyslop, 1999.
APP = β-amyloid precursor protein
PS1 = presenilin-1
PS2 = presenilin-2
ApoE = Apolipoprotein E
Aβ = amyloid-β peptide

Recent work has focused on cellular and immunologic mechanisms to decrease the production of beta-amyloid and/or increase its clearance once deposited. As noted, beta-amyloid itself comes from the APP and is formed by the action of three enzymes known as secretases—alpha, beta and gamma secretase. Identification of these secretases has been the goal of many researchers as identification is a prelude to the development of possible inhibitors, which would then inhibit the formation of beta-amyloid. In 1999 four pharmaceutical companies (Smith-Klein-Beechum, Amgen, Pharmacia and Upjohn, and Elan Pharmaceuticals) all identified the beta-secretase genes (Phimister, 2000), and in June of 2000, gamma secretase was identified as the protein presenilin (De Strooper, 2000). With remarkable rapidity, the first of the secretase inhibitors entered Phase I clinical trials in humans in 2000 (Nash, 2001). No results of human studies have been published.

Concurrently another group of researchers has been developing immunologic mechanisms to clear amyloid once it has been deposited. In 1999, Schenck and colleagues from Elan Pharmaceuticals reported that immunization of mice transgenic for APP with a "vaccine" containing beta-amyloid resulted in a decrease in plaque formation (Barinaga, 1999; Blass, 1999; Duff, 1999; Heemels, 2000; Hillery, 1999; Novak, 1999). In older mice with established plaques, use of the vaccine actually caused the plaques to disappear. These findings have stimulated additional research on determining possible adverse events from such a vaccine and on the usefulness of the vaccine in humans. Indeed human trials of the vaccine are now ongoing. Since the meeting of our Neurological expert panel, two independent research teams have reported that the vaccine also improves mental function in mice with experimental Alzheimer's-like disease (Janus et al., 2000; Morgan et al., 2000).

Other therapies. There are currently two FDA approved drugs that have demonstrated efficacy in patients with Alzheimer's disease: tacrine and donepezil. Both have been shown in randomized placebo-controlled clinical trials in humans to have statistically significant, albeit modest, effects at preserving cognitive function in people with mild to moderate AD. Both of these drugs are acetyl-cholinesterase inhibitors. There are many additional drugs that affect the

cholinergic system and other biochemical systems that are awaiting FDA approval or undergoing Phase III trials, including new acetyl- cholinesterase inhibitors, post-synaptic muscarinic receptor agonists, and stimulators of acetyl-choline release (Table A.21). However, none of these drugs have yet reported results that could be characterized as a breakthrough in the treatment of Alzheimer's disease (Emilien et al., 2000; Mayeux and Sano, 1999).

Table A.21. Relevant Drugs for Alzheimer's Disease Awaiting Approval or Undergoing Phase III Trials

Drug	Action
Awaiting Approval	
Trichlorfon	AChE inhibitor
Physostigmine salicylate	AChE inhibitor
Idebenone	Antioxidant
Nebracetam	m1 Muscarinic receptor agonist
Nefiracetam	m1 Muscarinic receptor agonist
Propentofylline	ACh agonist, calcium channel opener, and phosphodiesterase inhibitor
Undergoing Phase III Trials	
Amiridine	AChE inhibitor
Eptastigmine	AChE inhibitor
Galantamine	AChE inhibitor
Cevimeline hydrochloride	m1 Muscarinic receptor agonist
Talsaclidine	m1 Muscarinic receptor agonist
Dehydroepiandrosterone	Neurosteroid
Montirelin hydrate	ACh release stimulator, protirelin agonist
NS-105	ACh and GABA modulator
Selegiline hydrochloride	Monoamine oxidase B inhibitor
Taltirelin hydrate	Protirelin agonist

SOURCE: Emilien et al., 2000.

Additional research has been conducted on the modulation of other neurotransmitter systems. There is some evidence that neurotoxic excitatory amino acids may contribute to cognitive deficits in patients with AD. These excitatory amino acids, which are primarily glutamate, affect

cells through several receptors, one of which is *n*-methyl-D-aspartate (NMDA). Successful development of an antagonist to this and similar receptors would block the contribution of excitatory amino acids towards advancing cognitive decline. Several NMDA antagonists are currently in development or undergoing early clinical trials (Emilien et al., 2000).

A variety of neurotropic growth factors are in development, as nerve growth factor is associated with the maintenance of the function of the cholinergic system. Laboratory studies have demonstrated that some orally active agents have produced increases in nerve growth factors and there are reports of one compound (AIT-082) that affects memory in animals (Rivas-Vazquez et al., 2000), but reports of clinical effects in humans are lacking.

A variety of different anti-inflammatory agents have been proposed as possible Alzheimer's disease therapies. Retrospective analyses have described an inverse association between the use of anti-inflammatory drugs for other reasons (e.g., arthritis) and the development of AD. However, one randomized placebo-controlled clinical trial in 44 patients with Alzheimer's disease reported disappointing results (Rogers et al., 1993). An additional randomized clinical trial of 138 patients given either prednisone or placebo also did not report any statistically significant results favoring the use of prednisone (Aisen et al., 2000). Still, a variety of anti-inflammatory pharmacotherapies are in development.

There is a large body of evidence, some of it conflicting, that estrogen therapy helps prevent cognitive decline (Henderson et al., 2000). A recent clinical trial of short-term estrogen treatment in women did not report improvement. However, the long-term effects of estrogen therapy remain to be studied, as well as the effects of estrogen to prevent the onset of AD. The role of estrogen in preventing cognitive decline was reviewed in our Medical Technical Expert Panel on Breakthroughs in Cancer and the Biology of Aging.

Lastly, a variety of drugs designed to reduce oxidative stress have been proposed as therapies for Alzheimer's disease. Vitamin E, idebenone, ginkgo biloba, and experimental antioxidants are in development or clinical trials. However, human results have been mixed and have not been at a threshold that would warrant characterizing their efficacy as a "breakthrough" in treatment (Emilien et al., 2000; Mayeux and Sano, 1999; Rivas-Vazquez et al., 2000).

Table A.22. Classes of Drugs in Preclinical or Early Clinical Development for the Treatment of Alzheimer's Disease (AD)

Mechanism of Action	Drug	Comment
		Antiexcitotoxins
NMDA antagonist	L-701252	Being developed for treatment of AD, epilepsy, and cerebrovascular ischemia
NMDA antagonist	LY-235959	Competitive antagonist; potential for use in AD and other CNS diseases
NMDA antagonist	WIN-63480-2	Uncompetitive antagonist
		Neurotrophic
NGF agonist	AIT-082	Undergoing phase II clinical trials
NGF agonist	AK-30-NGF	Monoclonal antibody
NGF agonist	NBI-106	Potent immune stimulation and memory-enhancing properties
NGF agonist	rhNGF	Recombinant protein; also undergoing phase III clinical trials for peripheral neuropathy therapy
		Hormonal
Estrogen	ABPI-124	Specific for CNS; does not interact with other tissues
Estrogen	Neurestrol	An estrogen agonist developed by Endocon Inc., South Walpole, Mass, for treatment of women with AD
		Anti-inflammatory
Anti-inflammatory agent	SC-110	Undergoing phase 1 clinical trials
Cox 2 inhibitor	GR-253035	Entering phase 1 clinical trials for treatment of AD
Cytokine modulator	NBI-117	Reported to bind and activate newly discovered receptors of cytokine activin
		Antioxidants
Antioxidant	ARL-16556	Spin-trapping effects that scavenge free radicals and the ability to modulate the effects of nitric oxide indicate that it may have advantages over existing compounds; undergoing phase 1 clinical trials
Antioxidant	MDL-74180DA	Undergoing preclinical trials; analog of vitamin E that inhibits in vitro and ex vivo lipid oxidation and protects mice against CNS trauma

SOURCE: Emilien et al., 2000.
NOTES: AD= Alzheimer's Disease; NMDA = N-methyl D-aspartate; CNS = central nervous system ;Cox = cyclooxygenase; IC50 = the inhibition concentration at 50 percent; NGF = nerve growth factor; rhNGF = recombinant human NGF

*Likelihood of occurrence means widespread use in clinical practice.

Identification of high-risk individuals and the primary prevention of Alzheimer's disease. The gene encoding apolipoprotein E (ApoE) is a known susceptibility gene for typical Alzheimer's disease. Additionally, rare, early onset AD is associated with specific mutations in APP or presenilin, leading to overproduction of beta-amyloid (Roses, 2000). Major research programs are seeking to identify more genetic associations or causes of AD, in an effort to identify appropriate targets for pharmacotherapy. An additional benefit of such work may be the availability of blood tests to identify persons at high risk of developing AD, if an effective preventive therapy is developed.

The literature regarding primary prevention of AD by drugs that retard the aging process in general or cognition in specific (SERMs) was summarized above in the review for the Medical Technical Expert Panel on Breakthroughs in Cancer and the Biology of Aging. Prevention of Alzheimer's disease by interventions related to the amyloid hypothesis was reviewed above. Table A.22 summarizes the drugs in development for treating Alzheimer's disease.

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder of middle and older age, and effects about 1 percent of people over the age of 60. It is characterized by the symptoms of muscle rigidity, tremor, and dyskinesia. The cause is unknown. The fundamental pathologic abnormality is loss of dopaminergic neurons in the area of the brain known as the substantia nigra, causing dopamine depletion and deterioration of motor function. Dopamine replacement ameliorates the symptoms of the disease, but does not affect the underlying progression and is further limited by the development of dyskinesia. Therefore, research has aimed at developing means to replace the dopaminergic neurons in the substantia nigra.

One such technique is neurotransplantation. In 1992 three research groups reported results from transplantations of human fetal neural tissue into patients with PD (Freed et al., 1992; Spencer et al., 1992; Widner et al., 1992). Positron emission tomography demonstrated survival of the transplanted tissues up to 46 months after transplantation and modest to marked clinical improvement in most patients (Freed et al., 1992). These reports led to further research in neurotransplantation (Baker et al., 1997; Clarkson and Freed, 1999; Tabbal, Fahn, and Frucht, 1998), including the funding of a randomized sham controlled clinical trial of such therapy (Freed, Breeze, and Fahn, 2000). This study was recently completed but has yet to be reported. The main limitation to the more widespread use of neurotransplantation is ethical issues in collecting human fetal embryonic cells, which come from voluntary abortions. The use of cells from other species has been considered but such xenotransplants also raise ethical issues; in particular, the theoretical risk of cross-species transfer of animal retroviruses, which is the presumptive mechanism for the development of HIV in humans. More promising is the ability to influence human mesenchymal cells into differentiating into neuronal cells which would allow the use of fetal cord blood, which is collected without risk to the newborn baby, or even an individual's own cells for transplantation.

Another strategy for increasing dopaminergic neurons is the use of gene therapy to stimulate the production of dopamine. Experiments on a rat model of PD have been mixed (Kang and Frim, 1999). However, since the meeting of the Neurological expert panel, researchers have reported the successful use of the gene for human nerve growth factor (that promotes dopamine

production) in reversing the motor deficits and nigrostriatal degeneration seen in Rhesus monkeys with experimental Parkinsonism (Kordower et al., 2000). There have been no human experiments to date of gene therapy for Parkinson's disease.

The serendipitous discovery that 1-methyl-4-phenol-1,2,3,6-tetrahydropyradine (MPTP) caused Parkinson's-like symptoms in young people who inadvertently injected this compound (Langston et al., 1983) has led to increased interest that environmental toxins may be a significant contributing factor to idiopathic PD in older adults. Five gene mutations have been identified using family pedigrees in which the inheritance of a Parkinson's disease-like syndrome is strong (A.23).

Table A.23. Gene Mutations Identified in Familial Parkinson's Disease

Gene	Chromosome	Inheritance	Phenotype
α-synuclein	4	Autosomal dominant	L-DOPA responsive, early onset PD
parkin	6	Autosomal recessive	L-DOPA responsive, juvenile onset PD
UCH-L1	4	Incomplete penetrance	Typical PD
4p haplotype	4	Autosomal dominant	L-DOPA responsive, PD or postural tremor
PARK3	2	Autosomal dominant	Similar to sporadic PD

SOURCE: Dunnett and Bjorklund, 1999.
NOTE: PD = Parkinson's disease.

The products of these genes and their possible roles in the development in PD have not been well established, neither has any additional toxin other than MPTP been identified as causing Parkinsonism in humans. Since the meeting of the expert panel there have been reports that the pesticides rotenone and paraquat cause Parkinson's-like symptoms in rodents (Maugh, 2001).

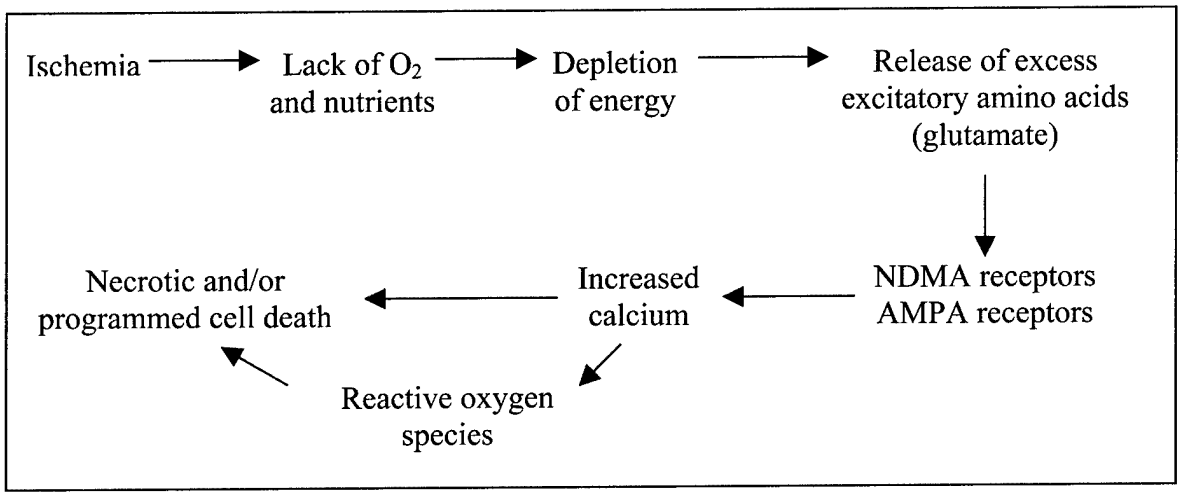
Treatment of Acute Stroke

Drugs given to minimize cell death (neuroprotective drugs). Stroke is the third leading cause of death in the United States and the leading cause of serious long-term disability. The first therapy shown to be effective at limiting the effects of an acute ischemic stroke was tissue plasminogen activator, based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) Study. This study of more than 600 patients randomized to receive either tissue plasminogen activator or placebo for acute ischemic stroke demonstrated modest to moderate improvements in disability at three months and six months (Fisher and Bogousslavsky, 1998). However, patients treated with tissue plasminogen activator had three times the rate of intracranial hemorrhage as did those treated with placebo. Other studies of thrombolysis did not report such positive results (Fisher and Bogousslavsky, 1998).

A model for the causes of cell death following acute ischemic stroke is depicted in Figure A.2. Important is that research has shown that cell death is due both to ischemic and necrotic death, but also due to programmed cell death (apoptosis) due to cellular signals transmitted as a

result of ischemia. In this model lack of oxygen and nutrients leads to the release of excitatory amino acids, mainly glutamate, which work through certain cellular receptors including N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA). This receptor activation leads to increased calcium and uncoupling of oxidative phosphorylation, and stimulates programmed cell death. This model suggests that it may be possible to limit the disability following acute ischemic stroke by decreasing the amount of programmed cell death that occurs in conjunction with ischemic cell death.

Figure A.2. Schematic Representation of Pathways to Cell Death Following Ischemic Injury



In animal stroke models extensive reductions of infarction volume were demonstrated with many different types of neuroprotective drugs. However, none of these therapies have been shown to be effective in humans, although research is still ongoing (Brott and Bogousslavsky, 2000; (Fisher and Bogousslavsky, 1998)). Some of the therapies that have been tried include calcium channel blockers, such as nimodipine, that has been shown in several clinical trials to be without benefit. However, it may be that these trials did not give the drug soon enough after the onset of stroke for any benefit to be evident, therefore there is currently an ongoing clinical trial in Europe where nimodipine is being given within six hours of the onset of ischemic stroke (Fisher and Bogousslavsky, 1998). Additional therapies targeted at the NMDA receptor also showed promise in animal studies; however, a Phase III clinical trial was stopped because of minimal benefit and possible excess risk (Fisher and Bogousslavsky, 1998).

Yet a third class of compounds that has been tried is those that inhibit the release of excitatory amino acids. Phosphenytoin has been shown to have neuroprotective properties in animal stroke models and is currently undergoing a Phase III clinical trial. Another compound in this class is lubeluzole, which has had disappointing results in both European and American Phase III trials. Antagonists against the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-receptor are also in development, but none has yet been shown to have beneficial effects in human stroke patients. Other neuroprotective therapies include the use of antioxidant and antileukocyte interventions. Again, success in animal models failed to translate into success

in human models. Various other therapies such as gamma-aminobutyric acid (GABA) and nitric oxide synthase inhibitors are undergoing early or even Phase III clinical trials. To date, although physiologically sound and successful in animal studies, no neuroprotective agent has yet been demonstrated to have significant "breakthrough" benefits for human stroke patients (Brott and Bogousslavsky, 2000; Fisher and Bogousslavsky, 1998).

Neurotransplantation of stem cells. The British biotechnology company ReNEURON announced at a press conference in the fall of 2000 that it was undertaking a small clinical trial of selected patients with stroke using immortal human stem cells to try and restore function (Reaney, 2000). The company claims that animal studies of such cells injected into the brains of rats with experimental stroke restored function. No results have yet been reported from this treatment.

Depression

Major depressive disorder, also called depression, has a lifetime risk ranging from 10 to 25 percent and from 5 to 12 percent in men with anywhere between 2 and 10 percent of people affected at any one time. Depression is associated with an increased mortality due to suicide and also through its interactions with other medical illnesses. Over 60 percent of suicides are attributed to major depressive disorder. Estimated annual costs are around $44 billion (Mulrow et al., 1999). There are three therapies proven effective for depressive disorders: pharmacotherapy, psychotherapy, and electroconvulsive therapy. The great majority of research is in developing newer pharmacotherapies. Existing anti-depressive pharmacotherapies affect the norepinephrine or serotonin pathways. New research on other existing neurotransmitters offers the possibility of improved pharmacologic treatment of depression. The following two compounds were highlighted by our expert panel.

Substance P, which was discovered 70 years ago, has recently emerged as a potential target for anti-depressant therapy. Studies have shown that the receptor for Substance P (NK_1) is concentrated in those areas of the brain that are responsible for the regulation of affective behavior and the neurochemical response to stress. In a guinea pig model, the infusion of Substance P agonists caused behavior similar to that caused by stress, whereas infusion of Substance P antagonists inhibited stress-related behavior. One randomized clinical trial in humans of a Substance P antagonist, MK-869, has been reported (Kramer et al., 1998). This was a multicenter randomized parallel group trial of MK-869, paroxetine (a serotonin mediated anti-depressant), and placebo in 198 patients with major depressive disorder and moderately high anxiety. The primary outcome was the 21 item Hamilton Depression Score. At six weeks after starting therapy, both MK-869 and paroxetine had statistically significant and equivalent benefits in terms of improvement. Patients treated with MK-869 had a 4.3 point improvement on the Hamilton Depression Score while patients treated with paroxetine had a 3.6 point improvement. The safety and tolerability of MK-869 were generally similar to those of the placebo. Important is that the incidence of sexual dysfunction in patients receiving MK-869 was no different than that in patients on placebo; whereas the incidence for patients receiving paroxetine was 26 percent (sexual dysfunction being a relatively common side effect of treatment with serotonin re-uptake inhibiting anti-depressant therapy). These findings provide clinical evidence that Substance P antagonism is an effective therapy for major depressive disorder and that it may be better tolerated than existing anti-depressive therapies.

Corticotropin Releasing Factor (CRF) is a small peptide originally discovered 20 years ago and known to be involved in behavioral responses to stress. Animal studies have shown that the central infusion of CRF produces behavior similar to that observed after exposure to stress. It has been hypothesized that chronic CRF hypersecretion leads to compensatory down regulation of CRF binding in the frontal cortex of the brain and that this pattern is associated with depression. Animal models of CRF antagonists demonstrate that their administration reduces stress or anxiety behavior normally observed in stressful situations (Owens and Nemeroff, 1999). No human studies have yet been reported. Table A.24 summarizes the evidence on all the breakthroughs identified by the neurological expert panel.

Table A.24. Evidence Table of Breakthroughs in Neurological Diseases

Breakthrough	Status of Development	Potential Barriers
Better identification of persons at increased risk	Genetic mutations are known to cause certain rare forms of Alzheimer's disease.	Multiple genes may be involved in the common variety of Alzheimer's disease, making their identification and interaction difficult.
Primary prevention of Alzheimer's disease utilizing compounds based upon the amyloid hypothesis	Successful studies of vaccine in mice. Secretase genes have been identified; inhibitors are in preclinical development.	Safety and efficacy in human studies.
Primary prevention of Alzheimer's disease utilizing existing or new drugs/ compounds	Numerous compounds postulated.	Very long lead time needed for human studies to demonstrate benefit.
Treatment of established Alzheimer's disease by vaccine, secretase inhibitor, antioxidants, anti-inflammatories, or SERMs	Successful studies of the vaccine in mice. Ongoing studies of vaccine in humans. One secretase inhibitor has entered phase I human trials. Many antioxidants, anti-inflammatories, and SERMs are in human clinical trials. Results that have been reported have been disappointing.	Safety and efficacy in human studies.
Treatment of established Alzheimer's disease by cognition enhancers	Numerous compounds in clinical trials; however. these have reported only modest, rather than "breakthrough," results at present.	Safety and efficacy in human studies.
Treatment of Parkinson's disease by neurotransplantation	Case series studies reporting in humans, one RCT completed but not reported.	Source of cells, ethics of xenotransplantation.
Prevention and treatment of Parkinson's disease by profiling genetic predisposition for susceptibility to environmental toxins.	One toxin has been shown to cause Parkinson's-like disease in humans. Additionally, experimental research on rodents has identified pesticides as potential causes of Parkinson's disease.	Some agents may be toxic only in combination with other agents. Understanding this complex interplay will be difficult.
Treatment of acute stroke by drugs given to minimize cell death.	Numerous drugs studied in human clinical trials; howeve,r results have been disappointing to date.	Safety and efficacy in humans.
Treatment of acute stroke by use of stem cells to restore neurological function	One announced case series in humans ongoing.	Demonstration of efficacy. Ethics of source of stem cells.

Table A.24

Evidence Table of Breakthroughs in Neurological Diseases, continued

Breakthrough	Status of Development	Potential Barriers
Better treatment of depression by existing or new drugs	Numerous drugs in animal models and human clinical trials. One reported RCT demonstrating benefit of substance P equal to that of established antidepressant therapy, but with fewer side effects.	Efficacy and safety in humans.

HEALTH SERVICES

Improvements in the Organization and Delivery of Health Services

As the delivery of health care becomes increasingly complex, information systems that can assist providers in making clinical decisions will become critical for delivering dependable, high-quality, evidence-based care. In 1998, the Committee on the Quality of Health Care in America, established within the Institute of Medicine (IOM), was appointed to identify strategies for achieving substantial improvement in the quality of health care in America. The committee's first report, *To Err is Human: Building a Safer Health System*, was released in November 1999 and focused on quality concerns relating to patient safety (Kohn, Corrigan, and Donaldson, 1999). The report indicated that 44,000 to 98,000 people die in U.S. hospitals each year as a result of medical errors, making them the eighth to fifth leading cause of death in the United States. The report also estimated that medical errors cost the United States approximately $38 billion per year, with about $17 billion of those costs associated with preventable errors.

In March 2001, the Committee on the Quality of Health Care in America released its second and final report, *Crossing the Quality Chasm: A New Health System for the 21st Century*, which addressed a broad range of quality issues and provided a strategic direction for redesigning the health care delivery system (Corrigan, Donaldson, and Kohn, 2001). The committee reported that the U.S. health care system is an outmoded and inadequate health care delivery system that is not capable of providing consistent, high-quality care to its population. In order to achieve safe, dependable, high-quality health care, a significant redesign of our systems will have to occur, and information technology (IT) must play a key role if substantial improvements in quality are to be achieved. The solution lies in redesigning systems of care to make it easier for health care providers and patients to make the best possible, evidence-based, clinical decisions. These changes will require the use of information systems, organizational changes in the health care delivery system, workflow redesign, and changes in reimbursement mechanisms.

It has been established that well-known, effective interventions that can reduce morbidity and mortality are significantly underutilized in health care. For example, use of the influenza vaccine in elderly populations has been shown to decrease morbidity, mortality and health care costs. In addition, it is inexpensive, easy to administer, and has relatively few and mild side effects. Yet approximately 50 percent of the eligible elderly population goes unvaccinated each year (Nichol et al., 1994). Another example is the use of beta-blockers in patients with myocardial infarction. There is strong evidence that use of beta-blockers in these patients can substantially reduce mortality. Yet, only about 50 percent of eligible patients receive this life-saving medication when indicated (McLaughlin et al., 1996). A third example can be seen in the use of aspirin in patients with diabetes. Patients with diabetes are at high risk for developing cardiovascular disease (CVD), and ischemic heart disease is the leading cause of death in patients with diabetes. There is good evidence that regular use of aspirin can reduce mortality in patients with CVD. Yet, only 39 percent of diabetic patients with a history of a myocardial infarction, 37 percent of diabetic patients with established CVD, and 13 percent of diabetic patients without CVD but with risk factors for CVD used aspirin on a regular basis (Rolka, Fagot-Campagna, and Narayan, 2001).

There are many other examples throughout the literature of inappropriate utilization of health care interventions, which can have a negative effect on quality of care and outcomes. In the vast majority of cases, these suboptimal care patterns do not result from individual clinician negligence or incompetence. They result from an overwhelming amount of medical information, rapid growth in new medications and technologies, increasing time constraints placed on providers, mounting pressures to reduce costs, and poorly designed systems for delivering care, which make it virtually impossible for clinicians to provide high-quality, error-free care on a consistent basis.

In response to this challenge, several institutions have harnessed the data processing capacity of computer systems to develop electronic medical record (EMR) systems with computerized physician order entry (CPOE) and clinical decision support. These systems range from computerized reminders about preventive services to alerts about drug-drug interactions to complex computerized ventilator management. Studies from these institutions provide evidence that use of CPOE with clinical decision support can reduce medication errors, reduce adverse drug events, increase use of preventive services, increase compliance with recommended guidelines, improve physician performance, and improve quality of care (Evans et al., 1995; Evans et al., 1998; Overhage et al., 1997; Bates et al., 1998; Teich et al., 2000; Hunt et al., 1998; Walton et al., 2001). Despite these successes, only a small number of health care systems in the United States have such systems in place.

While recent innovations in information technology have been touted over the past several years, many of these applications have not been adequately evaluated in health care. For example, wireless hand-held computers such as personal digital assistants (PDAs) offer great potential as a portable communication source with the potential for decision support. In preliminary studies, these devices have been shown to improve the detection and prevention of adverse events in an ICU setting (Shabot, LoBue, and Chen, 2000). However, more research is needed in this area to evaluate their effects on important patient outcomes in various health care settings.

Other evolving technologies may also play a role in improving patient safety, especially in the area of medication management. Medication bar codes and automated medication dispensers are being utilized in some health care settings to reduce errors. The use of scannable patient bracelets containing drug, allergy, and other medical information is also being explored. Such devices could help ensure that medications, blood products, and other therapeutics are appropriately administered to patients. They could also be used to generate alerts about allergies, drug-drug interactions, and other potential problems before erroneous administration occurs. The Veterans Administration and Department of Defense have been leaders in the application and assessment of these technologies.

"Smart cards" are electronic devices the size of credit cards that store and process medical information on a microprocessor chip. The Department of Defense has been a leader in the use of this technology. In much the same manner that ATM cards allow consumers to access banking services from virtually anywhere in the world, these smart cards would give patients a portable means of carrying their medical information, which could then be accessed electronically by providers or health care facilities at disparate locations. Interactive smart cards could also generate alerts about potential adverse events resulting from medication and other types of

errors. While promising, this technology remains in development and has not been utilized or evaluated to a significant degree in the clinical setting.

The use of technology to collect and analyze patient data from remote sites and transmit the information to providers is currently being utilized in some facilities. Telemedicine can be used to provide electronic delivery of health care services to remote areas. This allows consultative expertise to be provided to areas where it is not locally available. For example, a specialist physician can utilize telemedicine technology to work with local health care providers to manage patients in remote areas without the need for the patients to travel hundreds of miles to attend the specialist's clinic.

Technology is also currently available that allows patients to collect important measurements, such as blood pressure, weight, pulmonary function tests, and certain laboratory tests, and transmit the information over telephone lines or wireless networks to their providers. In some cases, these applications can also provide evidence-based recommendations to the patients, based on an analysis of the data collected. For example, a patient with asthma can blow into a spirometer and measure his or her peak flow multiple times throughout the day. This information can then be downloaded and transmitted to the physician's office. Depending on the spirometry results, decision support tools can advise the patient (e.g., your peak flow has decreased more than 25 percent below your baseline—please call your doctor's office now) and notify the provider of a potential problem (e.g., your patient's peak flow is 180, which is 28 percent below his baseline level of 250). This triggers a message to the clinical nurse specialist to call the patient, which is transmitted to her via beeper, cell phone, or PDA.

While clinical informatics has the potential to greatly improve quality of care, much more work is needed in terms of implementation and evaluation of these technologies and their effect on important outcomes. Research is needed to evaluate IT tools that alert providers to information that may be critical to the provision of high-quality care, develop strategies to address barriers to successful adoption of innovative IT applications, document the costs and resources associated with the IT applications, and evaluate transferability to other health care settings.

APPENDIX B:

THE SOCIAL SCIENCE EXPERT PANEL

The Social Science technical expert panel was designed to provide general oversight of all aspects of the project. More specifically, the responsibilities of this panel included:

- Determining appropriate health status measures
- Finding suitable methodologies to estimate model parameters
- Identifying data sets
- Assisting in model development
- Implementing what-if scenarios.

The panel members came from the fields of demography, epidemiology, health economics, actuarial science, and operations research. The panel met once, and this chapter summarizes its findings. Table B.1 shows the members of the panel.

Table B.1. Social Science Expert Panel

Name	Affiliation	Area(s) of Expertise						
		Medicine	Literature	Data Sets	Estimation	Health Status	Modeling	Scenarios
Joan Buchanan	Harvard University							
Eileen Crimmins	University of Southern California		X	X		X		X
David Cutler	Harvard University		X	X			X	
Jacob Feldman	Project HOPE		X	X		X		X
Vicki Freedman	Philadelphia Geriatric Center							
Michael Keane	New York University				X		X	
Emmett Keeler	RAND							
Mark McClellan	Stanford University	X		X	X			X
David Meltzer	University of Chicago	X				X		X
Joe Newhouse	Harvard University		X			X	X	X
Frank Sloan	Duke University		X	X				X

METHODS

For the social science literature review in Phase I, we identified "seed" articles from our own work, CMS's suggestions, and those recommended by our colleagues. We then conducted a systematic search for other references. This search was limited to articles published in 1989 or later, written in English, and applicable to the U.S. population/health care market. Using a sequence of searches, RAND identified over 5,000 relevant articles from reference databases. This list was then reviewed by the project team and a draft synthesis was prepared.

As part of Phase II, we convened a distinguished panel of social science experts to advise on all aspects of the project. Panel members were chosen from the fields of demography, epidemiology, health economics, actuarial science, and operations research. At the conclusion of the Phase I, the project team met with CMS staff and the social science panelists in March 2000. The design report and the draft literature synthesis were circulated prior to the meeting for review and comment.

The meeting followed the format of a research conference. It opened with a presentation on the research goals and timeline for all phases of the project. The four goals of the Social Science panel were then reviewed:

- **Provide feedback on the literature review.** Panelists were asked to assist in the review of the literature by answering the following questions: What evidence is missing? What conclusions can be drawn? Are there other modeling approaches to be considered? What disability scenarios should be simulated?

- **Advise on model development.** Panelists were given a copy of the modeling plans in advance as part of the final design report. At the meeting, several questions were submitted to the panelists: Is our approach feasible? Is it flexible enough to incorporate all the desired simulations? How should health status be measured? What is the best way to characterize disability? Should price changes be simulated?

- **Help integrate medical panel results**. Panelists were advised that parallel medical panels are identifying emerging technologies. These take the form of detailed treatment scenarios. The social scientists were asked to advise on how to build a model to forecast the consequences of these technologies. In particular, they were asked to advise on a trade-off between breadth (many scenarios) and depth (detailed clinical models). They were explicitly asked to consider alternatives to the approach identified in the final design report.

- **Identify key changes in health system**. As part of Phase I, leading geriatricians indicated that some of the key changes will not be from new technologies but rather from changes in health behavior and health delivery. The social scientists were asked to consider to what extent these kinds of changes can realistically be incorporated into the model? RAND offered example scenarios to prompt the panelists' response, including: Medicare policy changes, such as the addition of a prescription drug benefit and a long-term care benefit; continuation of current trends, including further movement into managed care and substitution of home care for inpatient; public health interventions,

such as extensive use of anti-obesity drugs or more screening for disease; behavioral modification, such as exercise and reduced fat intake; and changes in practice patterns, such as movement towards geriatric assessment and disease management and an emphasis on chronic care rather than acute treatment.

RAND then presented to the expert panel the results of the literature review. First, RAND described the measures of health status, followed by evidence on trends in disability. The panel then discussed current methods for forecasting expenditures by government agencies and compared these with other approaches suggested in the literature. In-depth discussion in each area ensued.

RAND then described in detail our proposed modeling approach to the panel. RAND explained our choice of a microsimulation projection method and presented the conceptual framework. Descriptions of the data, estimation, and forecasting methods followed. The discussion was focused on the feasibility and desirability of this approach.

In the afternoon, RAND discussed how to integrate new approaches into this microsimulation. A presentation of the purpose and content of the medical expert panels was given to the panelists. Discussion focused on how to translate the clinical scenarios into morbidity and mortality effects that could be incorporated into the model. The meeting concluded with a presentation and discussion of alternative conceptualizations of health status, disability, and cost estimation.

LITERATURE REVIEW

In Phase I, we examined how researchers have approached each stage of the modeling process, from selecting measures, to forming a baseline population, to predicting mortality, morbidity, and the cost of health care. We supplemented this review by revisiting relationships others have drawn to identify important contributors to these outcomes, and described points of contention and consensus on recent trends in mortality improvement and declines in disability.

RAND found that past projection efforts have varied widely in their level of sophistication, from relatively simple exercises where the modeler offers a scenario in which one factor (e.g., age distribution) is shifted holding all else in the world constant, and more intricate cell-based and microsimulation models where models attempt to capture some of the complexities of health and population dynamics. These latter models build a more complete picture of the world as they attempt to include more of the pathways and processes that move individuals forward from one health (and cost) state to the next. At first glance, this makes them more attractive and has the important advantage of improving the model's usefulness for incorporating uncertainty and scenario analysis (e.g., the Brookings-ICF model). But, our review reveals a natural trade off between gains in complexity and the need for additional—often implicit—assumptions about detailed processes. More detailed models also face more burdensome data requirements. As modelers meet these requirements by drawing on multiple data sets (e.g., Butler, Anderson, and Burkhauser, 1989) and as more assumptions are made it becomes more difficult to interpret, compare, and build on a model's results. Generalizability suffers as well.

There are two common remedies to this problem of interpretation and credibility of results, with a long history of successful application in other fields, including defense, aeronautics, manufacturing, and meteorology: 1) validation and 2) statistical rigor in running a simulation model and reporting results. Incorporating these practices in future projections would make them more convincing. While they are common in other fields and classic texts on simulation (e.g., Law and Kelton, 1982), they earned neither mention nor application in the simulation efforts reviewed here. First, model validation ensures that, at least for simple baseline scenarios, the model produces output that agrees with reality. For prediction, this means that for more complex scenarios one has some assurance that the model is valid. Second, simulations that include any uncertain components (e.g., hazards that rely on transition probabilities and random distributions of events that occur), will produce different results *each time* the simulation is run, so that it is essential to 1) run the model multiple times, 2) report how many iterations of the model were executed, and 3) report the *distributional properties* of the results to clarify their interpretation.

Past efforts choose a broad range of health measures as predictors of utilization and cost. Generally, physical functioning, self-reported general health, and the presence of symptoms and medical conditions have received the most attention, while measures of cognitive and mental functioning have largely been ignored. This can be attributed to the availability of the former measures in survey data and their intuitive appeal. However, a number of national surveys and instruments on cognitive and mental functioning are now available—and the costs of treating mental illnesses is rising—suggesting these data could be used in future projections.

Among the more common measures, self-reported general health, while an excellent predictor of cost, poses problems for interpretation. Most notably, it may impede efforts to model how *changes* in that measure will lead to changes in utilization of health services and cost. The literature review also uncovered problems with the wording and consistency of ADL and IADL measures of physical functioning between surveys. If these are to be used for projection, researchers need to select their measures—and merge similar measures from multiple surveys—according to the wording of the measures themselves rather than the words used by others to describe them (e.g., "functional limitations" vs. limitations in "activities").

The combined review of projection models and health measures suggests another promising area for improvement. When building projection models, researchers do not always begin from a broad conceptual model of the health process. However, a conceptual model that offers well-defined terminology for explicit pathways from pathology to disablement and back again with feedback loops, like Verbrugge's Disablement Process, provides a common ground for researchers to more fully and carefully assess their approach. Though defensible on their own, the projections reviewed here are disparate. They are difficult to compare and improve because they do not develop their hypotheses from a common conceptual foundation. Because the implementation of simulations alone generally blurs the clarity of results—as discussed above—future projections should at least begin from a common conceptual source that shares widespread acceptance and facile interpretation. A standard sociomedical model, such as The Disablement Process, is a good place to begin to strengthen comparability of results and clarify where future projections can best make effective contributions.

Finally, the literature relies mostly on extrapolation and scenarios that assume the relationship *between* variables will remain constant throughout the time horizon of projection.

These are the relationships that describe how changes in health, demographic, and other factors translate into changes in utilization and cost, which depend, among other things, on changes in individual behavior, medical practice, and advances in medical innovation. These relationships need not stay constant over time. In statistical regression terms, the coefficients themselves may be changing. Future projections may help to predict these changes or they may look to experts for estimates of what future trends will be. If they do, they will begin an important discussion mostly absent from the projections reviewed here. However, as noted by Alho (1990), expert opinion on its own may contribute little to the accuracy of predictions.

IMPLICATIONS FOR FUTURE WORK

The panelists made many suggestions on how to improve the scope and methods of the project. Specific areas they addressed were modeling issues, policy issues, measurement of health and disability, data, treatment of long-term care, and incorporating technology shocks.

Modeling

The panelists suggested producing a baseline model. This would be a simple cell-based approach that holds fixed current levels of technological change that may alter average costs within cells. This approach provides a baseline for calibration and comparison with the more sophisticated models currently contemplated by the RAND team. The panelists also suggested starting with a detailed theoretical framework. While they generally agreed with the broad outlines of the model that RAND is currently contemplating, they requested more detail on the definition of health/disability states in each period, and on the predictors that will be used to estimate costs.

The model should also distinguish changes in underlying health and disability from the relationship between these states and per-period costs. The panelists stressed the importance of considering the effects of changes in technology on the relationship between disability/disease status and costs of treatment, as well as on trends in disability/disease status. Trends in this relationship are not modeled in the current actuarial forecasts, and would thus represent a significant advance.

Several panelists argued that incorporating future changes in labor force participation would increase the precision and realism of the model considerably. They suggested distinguishing acute disease incidence from diseases that lead to chronic conditions and argued that the model should distinguish two different types of health events in the model. Acute health events, such as a cold, may lead to health care expenditures in the immediate period, but do not necessarily affect a patient's future health care state. More severe events may lead to future changes in health states, such as worsening a preexisting disability or chronic disease.

They considered it important to include risky health behaviors, such as smoking, in the model predicting costs. Race, education, and patient cognitive status were also commonly mentioned as important predictors. Beyond that, there was little consensus, with some panelists arguing for a "kitchen sink" approach—include all variables that potentially explain expenditures—whereas others argued that only explanatory variables that are likely to change over time should be included.

The panelists generally agreed that it was reasonable to assume that Medicare prices track private market prices. Some pointed to the growing importance of the non-elderly disabled in the Medicare budget: they comprise 15 percent of total expenditures. However, the panelists agreed that this population would require an entirely different model than the one for the elderly.

Policy

The panel argued against any type of political modeling because of the difficulties inherent in such predictions. Instead, they argued that the model should assume that the structure of future Medicare benefits will look similar to its current structure. Some of the panelists argued that the model should take into account recent changes in Medicare policy, and changes that are likely to happen. Examples of such policies include the development of the Medicare plus Choice plan, Medicare managed care options, and the possible adoption of an outpatient prescription drug benefit.

Health Measurement

General health measures based on a Likert scale—Excellent, Very Good, Good, Fair, Poor—were dismissed as inappropriate in a forecasting model of this type. Panelists stressed the importance of using a definition of disease state that is medically justifiable, with high face validity. The list of states should be exhaustive and mutually exclusive. There seemed to be agreement that health states in the model should combine disease and disability information. The panelists argued that the main advantage of using disease to define health state is that it will allow a direct translation of the information from the medical panels into predictions using the health transition/cost model. The main disadvantage is that disease does not necessarily explain costs, nor predict future health states. One panelist gave an example of the early diagnosis of cancer. Cancer can either be a positive or negative predictor of mortality depending on the type of cancer. For example, the early diagnosis of prostate cancer may indicate more health consciousness. Disability, on the other hand, is a better predictor of costs.

Disability Measurement

The panelists argued that disability should be viewed as a process that unfolds over time, so the model should be careful to distinguish among different stages of disability. Further, they cautioned against confusing disability with deficits in strength, gait, etc. Instead, they suggested a definition of disability that emphasizes the inability to perform normal tasks as a result of these deficits. Several panelists argued that it was important to make a distinction between assisted and unassisted disability. The latter measure is a more accurate assessment of the intrinsic physical ability of the patient, while the former may be more predictive of costs. Some argued that choosing carefully among definitions of disability is not important as long as all the measures have the same general relationship to the costs of treating the disease. For forecasting, measures of *average* improvement are the most relevant.

Data Issues

The panelists urged the use of panel data, rather than cross-sectional data, for forecasting purposes. They argued that the cross-sectional determinants of costs are not necessarily the same as the determinants of changing costs over time. However, one panelist argued that there were

unique changes in some subcategories of Medicare expenditures in the 1993–1997 period that are unlikely to hold into the future. The panelists generally agreed that this might bias predictions about the anomalous subcategories, and needs further investigation.

The panelists argued about the relative quality of self-reported versus claims data. The former better reflects the subjective view of patients about their health status, and thus may better predict costs, while the latter is more objective, but may be subject to bias due to over-reporting of high reimbursement conditions. The panelists cautioned that prevalence estimates may be very sensitive to the type of data being used.

The panelists agreed that it is appropriate to use the MCBS data set for the analysis. However, several pointed out a number of caveats regarding the MCBS. First, the MCBS generally reports higher rates of disability than do other surveys of the same population. In particular, patients in the MCBS are much more likely to report an inability to walk. The other disability questions in the MCBS do not suffer from this problem. Second, mortality rates calculated using the MCBS tend to be slightly high. Third, the MCBS respondents answer health status questions late in a calendar year (November). Thus, the health status questions in the MCBS should be used to predict medical expenditures in the following year, not the current one. Finally, the estimation should adjust for nonresponse and attrition.

Some panelists recommended caution about merging due to differences in how disability is assessed in different data, and differences in the population of surveyed people. Panelists liked the idea of using the other panel data sets to observe changes and trends in health status.

Treatment of Long-Term Care

Is nursing home care a predictor of costs or an outcome? The panelists debated whether nursing home care should be modeled as an outcome that arises due to poor health and disability, or as an independent predictor of costs. Most seemed to agree that nursing home care should not be included as an independent predictor. The panelists pointed out that most long-term care in nursing homes is not paid for by Medicare, while the short-term post-hospitalization stays often are. These need to be distinguished if nursing home care is separately modeled from other Medicare costs.

The panelists argued that among the principal explanations of changes in nursing home expenditures include increased longevity of spouses, the increased use of assisted living, and changes in elderly cognitive function.

Incorporating Technological Shocks

The panelists argued that there is tremendous uncertainty regarding the possibility of any particular technological breakthrough. Instead, the panelists suggested thinking generically about the rate at which technological breakthroughs occur, and about the effects on disease incidence and severity, on mortality, on disability, and on costs that changes in technology generically induce. Most populations would not benefit equally from technological innovations. Even in a relatively egalitarian system like Medicare, those with the most wealth tend to benefit the most quickly from technological breakthroughs. In addition, the panelists argued that the

costs of technological breakthroughs vary over time—most expensive first and then steadily decreasing costs later.

The panelists cautioned against focusing only on breakthroughs that target today's diseases since they can only be forecast down to zero. But if there are technological breakthroughs—such as anti-aging drugs—that augment the quality or length of life by altering biological processes that are not currently contemplated as disease, a narrow focus on today's diseases will lead to biased estimates of future Medicare costs. Some panelists pointed to an analogy with mortality forecasting by the Social Security Administration (SSA). The SSA underestimates mortality in part because it uses a cause-elimination method to forecast mortality improvement—it has no mechanism for predicting gains unrelated to current causes. Other panelists are skeptical this point will be empirically important for short-term forecasts.

Finally, the panelists argued that it is futile to directly predict the effect of technological breakthroughs on all the outcomes in the model. Instead, they suggested consulting experts and the literature for the effects on immediate outcomes and then using knowledge about links between outcomes to examine the effects on the distal outcomes. For example, while it is difficult to estimate the effect of cholesterol-reducing drugs on the population prevalence of people with difficulty performing ADLs, it is relatively easy to find the effect of these drugs on heart disease. This known effect on heart disease, coupled with a literature that discusses the correlation between heart disease and the future development of difficulty performing ADLs, will offer the most defensible and informed prediction based on current knowledge.

APPENDIX C:

NAMES AND AFFILIATIONS OF EXPERTS

Table C.1. Cardiovascular Diseases

Dr. Melvin D. Cheitlin
Emeritus Professor of Medicine at University of California, San Francisco.
Dr. Harlan Krumholz
Associate Professor of Medicine (Cardiology), Yale University School of Medicine.
Dr. Edward Lakatta
Director, Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health; Professor, Department of Physiology, University of Maryland School of Medicine; Professor, Cardiology Division, Johns Hopkins School of Medicine.
Dr. Eric Peterson
Associate Professor of Medicine, Division of Cardiology, Duke University School of Medicine.
Dr. Michael W. Rich
Associate Professor of Medicine, Washington University; Director, Cardiac Rapid Evaluation Unit, Barnes-Jewish Hospital.
Dr. Lynne W. Stevenson
Associate Professor of Medicine, Harvard Medical School; Director, Heart Failure Program, Brigham and Women's Hospital.

Table C.2. Biology of Aging and Cancer

Dr. Richard N. Bergman
Chairman of the Physiology Department and Director of the Diabetes Center, University of Southern California.
Dr. Judith Campisi
Senior Scientist and Director of the Center for Research and Education in Aging, Lawrence Berkeley National Laboratory.
Dr. William Ershler
Director, Institute for Advanced Studies in Aging and Geriatric Medicine, Washington, DC.
Dr. Caleb E. Finch
Professor of Gerontology and Biological Sciences, Andrus Gerontology Center, University of Southern California; Co-director, Alzheimer's Disease Research Center Consortium of Los Angeles and Orange Counties.
Dr. Richard A. Miller
Professor of Pathology, University of Michigan; Associate Director, University of Michigan Geriatrics Center; Senior Research Scientist, Institute of Gerontology.

Table C.3. Neurological Diseases

Dr. Dale E. Bredesen President and CEO, Buck Institute. *Dr. George M. Martin* Professor of Pathology and Adjunct Professor of Genetics, University of Washington School of Medicine; Associate Director, Alzheimer's Disease Research Center. *Dr. Howard Federoff* Professor of Neurology and Chief of the Division of Molecular Medicine and Gene Therapy, University of Rochester; Director, Center on Aging and Developmental Biology. *Dr. Jeffrey L. Cummings* Augustus S. Rose Professor of Neurology, Professor of Psychiatry and Biobehavioral Sciences, and Director of the UCLA Alzheimer's Disease Research Center, University of California, Los Angeles, School of Medicine. *Dr. Franz F. Hefti* Vice President, Merck Research Laboratories; Director, Neuroscience Research Centre, Merck Sharp & Dohme, Harlow, Essex.

APPENDIX D:

LITERATURE SEARCH STRATEGIES

Table D.1. Literature Search Strategy for Cardiovascular Diseases

SEARCH #1 NUMBER OF ITEMS RETRIEVED: 1870
TIME PERIOD COVERED: 1999-PRESENT
DATABASES SEARCHED: Pharmaceutical News Index
Internation Pharmaceutical Abstracts
Current BioTech Abstracts
Drug News & Perspectives
ESPICOM Pharm&Med DEVICE NEWS
F-D-C Reports
Adis Newsletters(Current)
Adis Newsletters(Archive)
Derwent Biotechnology Abstracts
SEARCH TERMS: [NOTE - A QUESTION MARK AFTER A TERM INDICATES TRUNCATION]
HEART FAILURE OR HEART DISEASE? OR HEART ATTACK? OR CORONARY OR ISCHEM? OR ISCHAEM? OR MYOCARDIAL INFARC? OR ATHEROSCLEROSIS OR HYPERTEN? OR ANTIHYPERTENS? OR ANTI HYPERTENS? OR ATRIAL FIBRILLAT? OR ARRHYTHM? OR DYSRRHYTHM? OR DISRHYTHM? OR STROKE? OR CEREBROVASCULAR DISORDER? OR CEREBROVASCULAR DISEASE? OR CEREBROVASCULAR ACCIDENT? OR TRANSIENT ISCH? ATTACK? OR LUSITROP? OR DIASTOLIC DYSFUNCTION? OR VASCULAR AGING
AND
GENE? OR NEW OR INNOVAT? OR BREAKTHROUGH? OR BREAK(2W)THROUGH? OR ENGINEER? OR BIOENGINEER? OR TECHNOLOG? OR BIOTECHNOLOG?

SEARCH #2 NUMBER OF ITEMS RETRIEVED: 1213
TIME PERIOD COVERED: 1999-PRESENT
DATABASES SEARCHED:
TGG Health&Wellness Database
SEARCH TERMS:
(HEART FAILURE OR HEART DISEASE? OR HEART ATTACK? OR CORONARY OR ISCHEM? OR ISCHAEM? OR MYOCARDIAL INFARC? OR ATHEROSCLEROSIS OR HYPERTEN? OR ANTIHYPERTENS? OR ANTI HYPERTENS? OR ATRIAL FIBRILLAT? OR ARRHYTHM? OR DYSRRHYTHM? OR DISRHYTHM? OR STROKE? OR CEREBROVASCULAR DISORDER? OR CEREBROVASCULAR DISEASE? OR CEREBROVASCULAR ACCIDENT? OR TRANSIENT ISCH? ATTACK? OR LUSITROP? OR DIASTOLIC DYSFUNCTION? OR VASCULAR AGING) - TERMS FROM TITLE OR SUBJECT HEADINGS FIELDS ONLY
AND
GENE? OR NEW OR INNOVAT? OR BREAKTHROUGH? OR BREAK(2W)THROUGH? OR ENGINEER? OR BIOENGINEER? OR TECHNOLOG? OR BIOTECHNOLOG?

SEARCH #3 NUMBER OF ITEMS RETRIEVED: 1703
TIME PERIOD COVERED: 1999-PRESENT
DATABASES SEARCHED:
Biosis Previews(R) (c) 2000 BIOSIS
SEARCH TERMS:
(HEART FAILURE OR HEART DISEASE? OR HEART ATTACK? OR CORONARY OR ISCHEM? OR ISCHAEM? OR MYOCARDIAL INFARC? OR ATHEROSCLEROSIS OR HYPERTEN? OR ANTIHYPERTENS? OR ANTI HYPERTENS? OR ATRIAL FIBRILLAT? OR ARRHYTHM? OR DYSRRHYTHM? OR DISRHYTHM? OR STROKE? OR CEREBROVASCULAR DISORDER? OR CEREBROVASCULAR DISEASE? OR CEREBROVASCULAR ACCIDENT? OR TRANSIENT ISCH? ATTACK? OR LUSITROP? OR DIASTOLIC DYSFUNCTION? OR VASCULAR AGING) - TERMS FROM TITLE OR SUBJECT HEADINGS FIELDS ONLY
AND
GENE? OR NEW OR INNOVAT? OR BREAKTHROUGH? OR BREAK(2W)THROUGH? OR ENGINEER? OR BIOENGINEER? OR TECHNOLOG? OR BIOTECHNOLOG?
AND
(DIAGNOS? OR TREAT? OR THERAP?)- TERMS FROM TITLE OR SUBJECT HEADINGS FIELDS ONLY

SEARCH #4 NUMBER OF ITEMS RETRIEVED: 193
TIME PERIOD COVERED: 1999-PRESENT
DATABASES SEARCHED:
Pharmaceutical News Index
Internation Pharmaceutical Abstracts
Current BioTech Abstracts
Drug News & Perspectives
ESPICOM Pharm&Med DEVICE NEWS
F-D-C Reports
Adis Newsletters(Current)
Adis Newsletters(Archive)
Derwent Biotechnology Abstracts
TGG Health&Wellness DB(SM)
Biosis Previews(R) (c) 2000 BIOSIS
SEARCH TERMS:
ANGIOGEN?
AND
HEART FAILURE OR HEART DISEASE? OR HEART ATTACK? OR CORONARY OR ISCHEM? OR ISCHAEM? OR MYOCARDIAL INFARC?

SEARCH #5 NUMBER OF ITEMS RETRIEVED: 1194
TIME PERIOD COVERED: 1999-PRESENT
DATABASES SEARCHED:
MEDLINE
HealthSTAR
Embase
[NOTE - AN EXCLAMATION POINT AFTER A TERM INDICATES THAT THE TERM WAS EXPLODED - I.E. SEARCHED HIERARCHICALLY]
SEARCH TERMS:
HEART FAILURE, CONGESTIVE! (MEDLINE,HEALTHSTAR) OR HEART FAILURE! (EMBASE) OR CARDIAC OUTPUT, LOW (MEDLINE,HEALTHSTAR) OR MYOCARDIAL ISCHEMIA! (MEDLINE,HEALTHSTAR) OR ISCHEMIC HEART DISEASE! (EMBASE) OR CORONARY ARTERY DISEASE! (EMBASE) OR ATHEROSCLEROSIS IN TITLE OR SUBJECT HEADING FIELD (MEDLINE,HEALTHSTAR) OR ATHEROSCLEROSIS! (EMBASE) OR HYPERTENSION IN TITLE OR SUBJECT HEADING FIELD (MEDLINE,HEALTHSTAR) OR HYPERTENSION! (EMBASE) OR ANTIHYPERTENSIVE AGENTS (MEDLINE,HEALTHSTAR) OR ANTIHYPERTENSIVE AGENT! (EMBASE) OR ATRIAL FIBRILLAT? OR ARRHYTHMIA! (MEDLINE,HEALTHSTAR) OR ARRHYTHM? (EMBASE) OR TACHYCARDIA! (EMBASE) OR ANTI ARRHYTHMIA AGENT? OR DYSRRYTHM? OR CEREBROVASCULAR DISORDERS!/MAJ (MEDLINE,HEALTHSTAR) OR CEREBROVASCULAR DISEASE! (EMBASE) OR ISCHEMIC ATTACK, TRANSIENT (MEDLINE,HEALTHSTAR) OR TRANSIENT ISCHEMIC ATTACK (EMBASE) OR LUSITROP? OR DIASTOLIC DYSFUNCTION? OR VASCULAR AGING
AND
GENETIC TECHNIQUES! (MEDLINE,HEALTHSTAR) OR GENE THERAPY (EMBASE) OR GENETIC ENGINEERING AND GENE TECHNOLOGY! (EMBASE)

SEARCH #6 NUMBER OF ITEMS RETRIEVED: 684
TIME PERIOD COVERED: 1999-PRESENT
DATABASES SEARCHED:
MEDLINE
HealthSTAR
SEARCH TERMS:
HEART FAILURE, CONGESTIVE! OR CARDIAC OUTPUT, LOW OR MYOCARDIAL ISCHEMIA! OR ATHEROSCLEROSIS IN TITLE OR SUBJECT HEADING FIELD OR HYPERTENSION IN TITLE OR SUBJECT HEADING FIELD OR ANTIHYPERTENSIVE AGENTS OR ATRIAL FIBRILLAT? OR ARRHYTHMIA! OR ANTI ARRHYTHMIA AGENT? OR DYSRRYTHM? OR CEREBROVASCULAR DISORDERS!/MAJ OR ISCHEMIC ATTACK, TRANSIENT OR LUSITROP? OR DIASTOLIC DYSFUNCTION? OR VASCULAR AGING
AND
DRUG THERAPY! OR DRUG THERAPY(SUBHEADING) OR INVESTIGATIONAL NEW DRUG APPLICATION OR DRUGS, INVESTIGATIONAL
AND
NEW OR BREAKTHROUGH? OR BREAK? THROUGH? OR INNOVAT? OR EXPERIMENT? OR BIOENGINEER? OR BIOTECH? OR ENGINEER?)

SEARCH #7 NUMBER OF ITEMS RETRIEVED: 4275
TIME PERIOD COVERED: 1999-PRESENT
DATABASE SEARCHED:
Embase
SEARCH TERMS:
HEART FAILURE! OR ISCHEMIC HEART DISEASE! OR CORONARY ARTERY DISEASE! OR ATHEROSCLEROSIS! OR HYPERTENSION OR ANTIHYPERTENSIVE AGENT! OR ATRIAL FIBRILLAT? OR ARRHYTHM? OR TACHYCARDIA! OR ANTI ARRHYTHMIA AGENT? OR DYSRRHYTHM? OR CEREBROVASCULAR DISEASE! OR TRANSIENT ISCHEMIC ATTACK OR LUSITROP? OR DIASTOLIC DYSFUNCTION? OR VASCULAR AGING
AND
DRUG THERAPY! OR DRUG DEVELOPMENT! OR DRUG RESEARCH OR NEW IN TITLE FIELD OR BREAKTHROUGH? OR BREAK? THROUGH? OR INNOVAT? OR BIOENGINEER? OR BIOTECH? OR ENGINEER?

SEARCH #8 NUMBER OF ITEMS RETRIEVED: 115
TIME PERIOD COVERED: 1999- PRESENT
DATABASES SEARCHED:
MEDLINE
HealthSTAR
Embase
SEARCH TERMS:
ANGIOGENE?
AND
HEART FAILURE, CONGESTIVE! (MEDLINE,HEALTHSTAR) OR HEART FAILURE! (EMBASE) OR CARDIAC OUTPUT, LOW (MEDLINE,HEALTHSTAR) OR MYOCARDIAL ISCHEMIA! (MEDLINE,HEALTHSTAR) OR ISCHEMIC HEART DISEASE! (EMBASE) OR CORONARY ARTERY DISEASE! (EMBASE)

SEARCH #9 NUMBER OF ITEMS RETRIEVED: see below
TIME PERIOD COVERED: 1999-PRESENT
DATABASES SEARCHED: Pharmaceutical News Index
Internation Pharmaceutical Abstracts
Current BioTech Abstracts
Drug News & Perspectives
ESPICOM Pharm&Med DEVICE NEWS
F-D-C Reports
Adis Newsletters(Current)
Adis Newsletters(Archive)
Derwent Biotechnology Abstracts
Search Terms:
LEFT VENTRIC? AND IMPLANT? AND ASSIST?
Number of Items Retrieved: 5
Search Terms:
(PIG? OR PORCIN? OR SWINE) AND (HEART? OR VALVE?) AND TRANSPLANT?
Number of Items Retrieved: 9
Search Terms:
HEART AND VALVE? AND (GROW? OR VITRO OR LABORATOR?)
Number of Items Retrieved: 46
Search Terms:
(MAGNETIC RESONANCE IMAG? OR MRI OR NUCLEAR MAGNETIC RESONANCE OR TOMOGRAPH?) AND (FAST OR ULTRAFAST OR ULTRA FAST) AND (HEART OR CARDIAC OR CORONARY OR ISCHE?)
Number of Items Retrieved: 71
Search Terms:
HYPERCHOLESTEROLEMIA OR HIGH CHOLESTEROL AND (GENE? OR DNA)
Number of Items Retrieved: 50

SEARCH #10 NUMBER OF ITEMS RETRIEVED: see below
TIME PERIOD COVERED: 1999-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
Embase
Search Terms:
(HEART ASSIST DEVICE(S) OR HEART LEFT VENTRICLE! OR LEFT VENTRIC?) AND (IMPLANT? OR IMPLANT! OR IMPLANTATION! OR MINIPUMP?)
Number of Items Retrieved: 126
Search Terms:
(TRANSPLANTATION, HETEROLOGOUS OR XENOTRANSPLANTATION OR HEART TRANSPLANTATION OR HEART VALVE(S)! OR HEART VALVE PROSTHESIS IMPLANTATION) AND (PIG? OR SWINE)
Number of Items Retrieved: 68
Search Terms:
VITRO AND (HEART VALVE(S)!
Number of Items Retrieved: 180
Search Terms:
(MAGNETIC RESONANCE IMAGING! OR TOMOGRAPHY, EMISSION-COMPUTED! OR TOMOGRAPHY, X-RAY! OR TOMOGRAPHY!) AND (MYOCARDIAL ISCHEMIA!(L)DIAGNOSIS OR CORONARY DISEASE!(L)DIAGNOSIS OR CORONARY ARTERY DISEASE!(L)DIAGNOSIS) AND (FAST OR ULTRAFAST OR ULTRA FAST)
Number of Items Retrieved: 28
Search Terms:
HYPERCHOLESTEROLEMIA! AND (GENETIC TECHNIQUES! OR GENE THERAPY OR GENETIC ENGINEERING "AND" GENE TECHNOLOGY!
Number of Items Retrieved: 171

SEARCH #11 NUMBER OF ITEMS RETRIEVED: see below
TIME PERIOD COVERED: 1999-2000
DATABASES SEARCHED:

Pharmaceutical News Index	International Pharmaceutical Abstracts
Current BioTech Abstracts	Drug News & Perspectives
ESPICOM Pharm&Med DEVICE NEWS	F-D-C Reports
Adis Newsletters(Current)	Adis Newsletters(Archive)
Derwent Biotechnology Abstracts	MEDLINE
HealthSTAR	Embase

Search Terms: BOSENTAN OR Ro 47-0203
Number of Items Retrieved: 6
Search Terms: BAY-Y5959 OR BAYY5959 OR BAY Y 5959
Number of Items Retrieved: 26
Search Terms: (FIBROBLAST GROWTH FACTOR 2 OR FGF2 OR FGF 2) AND (CORONARY ARTERY OR CAD)
Number of Items Retrieved: 6
Search Terms: TEDISAMIL
Number of Items Retrieved: 19
Search Terms: ANGIOPEPTIN OR LANREOTIDE
Number of Items Retrieved: 9
Search Terms: CVT 510
Number of Items Retrieved: 8
Search Terms: RHVEGF165
Number of Items Retrieved: 10
Search Terms: TENECTEPLASE? OR TNK TPA
Number of Items Retrieved: 40
Search Terms: L-159282
Number of Items Retrieved: 3
Search Terms: SR-33589
Number of Items Retrieved: 4
Search Terms: BRL-32872
Number of Items Retrieved: 4

Table D.2. Literature Search Strategy for Biology of Aging and Cancer

SEARCH #1 NUMBER OF ITEMS RETRIEVED: 397
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
SEARCH TERMS:
BREAST NEOPLASMS! OR BREAST CANCER! OR LUNG NEOPLASMS! OR LUNG CANCER! OR COLONIC NEOPLASMS! OR COLON CANCER! OR PROSTATIC NEOPLASMS! OR PROSTATE CANCER! - ALL MAJOR TERMS
AND
BIOMEDICAL ENGINEERING OR BIOMEDICAL TECHNOLOGY OR TECHNOLOGY, MEDICAL OR BIOENGINEERING! OR BIOLOGICAL THERAPY! OR BIOTECHNOLOGY OR TECHNOLOGY OR BREAKTHROUGH? OR BREAK? THROUGH? OR NEW OR INNOVAT? OR DISCOVER?
AND
DOCUMENT TYPE = REVIEW LITERATURE OR REVIEW, ACADEMIC

SEARCH #2 NUMBER OF ITEMS RETRIEVED: 272
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
SEARCH TERMS:
ANGIOGENESIS INHIBITOR(S) OR ANGIOGENESIS FACTOR OR ANGIOGEN?
AND
NEOPLASMS! OR MALIGNANT NEOPLASTIC DISEASE!

SEARCH #3 NUMBER OF ITEMS RETRIEVED: 177
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
SEARCH TERMS:
TELOMERASE IN TITLE OR SUBJECT HEADING FIELD
AND
DOCUMENT TYPE = REVIEW LITERATURE OR REVIEW, ACADEMIC

SEARCH #4 NUMBER OF ITEMS RETRIEVED: 240
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
SEARCH TERMS:
CANCER VACCINE?
AND
DOCUMENT TYPE = REVIEW LITERATURE OR REVIEW, ACADEMIC

SEARCH #5 NUMBER OF ITEMS RETRIEVED: 223
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
SEARCH TERMS:
SELECTIVE ESTROGEN RECEPTOR MODULATOR?

SEARCH #6 NUMBER OF ITEMS RETRIEVED: 457
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
SEARCH TERMS:
ALZHEIMER DISEASE-PREVENTION OR [ALZHEIMER DISEASE AND (PREVENTIVE MEDICINE! OR PREVENTION!)
AND
DOCUMENT TYPE = REVIEW LITERATURE OR REVIEW, ACADEMIC (NOTE- THIS LIMITATION WAS APPLIED TO EMBASE BUT NOT MEDLINE OR HEALTHSTAR)

SEARCH #7 NUMBER OF ITEMS RETRIEVED: 263
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
SEARCH TERMS:
AGING/MAJ OR CELL AGING OR SKIN AGING OR CELL AGING, CELL DEGENERATION AND CELL SURVIVAL
AND
GENETIC ENGINEERING AND GENE TECHNOLOGY!
OR
AGING, GENETICS
AND
DOCUMENT TYPE = REVIEW LITERATURE OR REVIEW, ACADEMIC

Table D.3. Literature Search Strategy for Neurological Diseases

SEARCH #1 (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 1660**
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
PsycINFO
EMBASE
SEARCH TERMS:
ALZHEIMER(S) DISEASE
AND
DOCUMENT TYPE = REVIEW OR REVIEW LITERATURE OR REVIEW, ACADEMIC FROM MEDLINE, HEALTHSTAR, EMBASE OR REVIEW? IN TITLE OR SUBJECT HEADING FROM PSYCINFO
AND
HUMAN
AND
ENGLISH

SEARCH #2: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 1003**
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
PsycINFO
EMBASE
SEARCH TERMS:
PARKINSON(S) DISEASE OR ANTIPARKINSON AGENT(S) OR ANTITREMOR DRUGS FROM PSYCINFO
AND
DOCUMENT TYPE = REVIEW OR REVIEW LITERATURE OR REVIEW, ACADEMIC FROM MEDLINE,HEALTHSTAR,EMBASE OR REVIEW? IN TITLE OR SUBJECT HEADING FROM PSYCINFO
AND
HUMAN
AND
ENGLISH

SEARCH #3: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 1350**
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
PsycINFO
EMBASE
SEARCH TERMS:
ANTIOXIDANT? OR ANTI(2W)OXIDANT?
AND
DOCUMENT TYPE = REVIEW OR REVIEW LITERATURE OR REVIEW, ACADEMIC FROM MEDLINE,HEALTHSTAR,EMBASE. [THE PSYCINFO RESULTS WERE NOT QUALIFIED TO REVIEWS BECAUSE THERE WERE RELATIVELY FEW OF THEM - RS]
AND
HUMAN
AND
ENGLISH

SEARCH #4: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 1870**
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
PsycINFO
EMBASE
SEARCH TERMS:
DEPRESSION OR DEPRESSIVE DISORDER! WITH SUBHEADING DRUG THERAPY FROM MEDLINE,HEALTHSTAR
OR DEPRESSION WITH SUBHEADING DRUG THERAPY FROM EMBASE
OR DEPRESSION IN TITLE OR SUBJECT HEADING AND (DRUG? OR MEDICATION? OR PHARMAC?) FROM PSYCINFO
OR ANTIDEPRESSIVE AGENTS FROM MEDLINE, HEALTHSTAR
OR ANTIDEPRESSANT AGENT! FROM EMBASE
OR ANTIDEPRESSANT DRUGS FROM PSYCINFO
AND
DOCUMENT TYPE = REVIEW OR REVIEW LITERATURE OR REVIEW, ACADEMIC FROM MEDLINE, HEALTHSTAR, EMBASE OR REVIEW? IN TITLE OR SUBJECT HEADING FROM PSYCINFO
AND
HUMAN
AND
ENGLISH

SEARCH #5: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 51**
DATABASES SEARCHED AND TIME PERIOD COVERED:
MEDLINE 1993-2000
HealthSTAR 1975-2000
PsycINFO 1887-2000
EMBASE 1993-2000
SEARCH TERMS:
ALZHEIMER(S) DISEASE
AND
VACCINES! FROM MEDLINE, HEALTHSTAR OR VACCINE FROM EMBASE OR VACCINATION FROM MEDLINE, HEALTHSTAR, EMBASE OR IMMUNIZ? IN TITLE OR SUBJECT FIELDS
AND
ENGLISH

SEARCH #6: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 21**
DATABASES SEARCHED AND TIME PERIOD COVERED:
MEDLINE 1993-2000
HealthSTAR 1975-2000
PsycINFO 1887-2000
EMBASE 1993-2000
SEARCH TERMS:
PARKINSON(S) DISEASE OR ANTIPARKINSON AGENT(S) OR ANTITREMOR DRUGS FROM PSYCINFO
AND
VACCINES! FROM MEDLINE, HEALTHSTAR OR VACCINE FROM EMBASE OR VACCINATION FROM MEDLINE, HEALTHSTAR, EMBASE OR IMMUNIZ? IN TITLE OR SUBJECT FIELDS
AND
ENGLISH

SEARCH #7: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 125**
DATABASES SEARCHED AND TIME PERIOD COVERED:
MEDLINE 1993-2000
HealthSTAR 1975-2000
PsycINFO 1887-2000
EMBASE 1993-2000
SEARCH TERMS:
SECRETASE? AND INHIBIT?
AND
ALZHEIMER(S) DISEASE
AND
ENGLISH

SEARCH #8: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 650**
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
PsycINFO
EMBASE
SEARCH TERMS:
(CEREBROVASCULAR DISORDERS! AND PREVENTIVE MEDICINE! OR THERAPY!) FROM MEDLINE, HEALTHSTAR
OR (STROKE WITH SUBHEADINGS PREVENTION & CONTROL OR THERAPY) FROM EMBASE OR (STROKE AND PREVENTIVE MEDICINE OR THERAPY) FROM EMBASE
OR (CEREBROVASCULAR ACCIDENTS AND PREVENTION IN TITLE AND SUBJECT FIELDS) FROM PSYCINFO
OR (CEREBROVASCULAR ACCIDENTS AND PREVENTIVE MEDICINE) FROM PSYCINFO
OR (CEREBROVASCULAR ACCIDENTS AND TREATMENT IN TITLE AND SUBJECT FIELDS) FROM PSYCINFO
AND
ACUTE
AND
ENGLISH

SEARCH #9: (PERFORMED 9/12/00) **NUMBER OF ITEMS RETRIEVED: 228**
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
SEARCH TERMS:
(CEREBROVASCULAR DISORDERS WITH SUBHEADINGS PREVENTION & CONTROL OR THERAPY)
AND
DOCUMENT TYPE = REVIEW OR REVIEW LITERATURE OR REVIEW, ACADEMIC

SEARCH #10: (PERFORMED 9/11/00) **NUMBER OF ITEMS RETRIEVED: 2**
DATABASES SEARCHED AND TIME PERIOD COVERED:
MEDLINE 1993-2000
HealthSTAR 1975-2000
PsycINFO 1887-2000
EMBASE 1993-2000
SEARCH TERMS:
ENDOGENOUS(3W)NEUROGENESIS

SEARCH #11: (PERFORMED 9/13/00) **NUMBER OF ITEMS RETRIEVED: 443**
TIME PERIOD COVERED: 1998-2000
DATABASES SEARCHED:
MEDLINE
HealthSTAR
PsycINFO
EMBASE
SEARCH TERMS:
NEUROGENESIS
AND
DOCUMENT TYPE = REVIEW OR REVIEW LITERATURE OR REVIEW, ACADEMIC FROM MEDLINE, HEALTHSTAR, EMBASE OR REVIEW? FROM PSYCINFO
AND
HUMAN

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